EXHIBIT D.

A copy of the FDA letter granting approval of the NDA to market ROZEREM™ (ramelteon), letter dated July 22, 2005.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-782

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, Illinois 60069

Attention: Tracy Lynch
Program Manager, Regulatory Affairs

Dear Ms. Lynch:

Please refer to your new drug application (NDA) dated September 21, 2004, received September 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rozerem (ramelteon) Tablets, 8 mg.

We acknowledge receipt of your submissions dated November 16, 2004, and January 14 and 20, February 4, 15, and 22, March 7, 17, and 23, April 4 and 21, May 12, June 1, 2, 15, 22, 24, 28, and 30, and July 8, 18, and 22, 2005.

This new drug application provides for the use of Rozerem (ramelteon) Tablets for the treatment of insomnia characterized by difficulty with sleep onset.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and carton and immediate container labels, submitted July 22, 2005). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format-Content of Labeling*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-782.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 through 16 years until July 22, 2012.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered a required postmarketing study commitment. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of insomnia characterized by difficulty with sleep onset in pediatric patients ages 0 through 16.

   Final Report Submission: July 22, 2012

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anesthesia, Analgesia, and Rheumatology Products and two copies of both the promotional materials and the package insert directly to:

> Division of Drug Marketing, Advertising, and Communications, HFD-42
> Food and Drug Administration
> 5600 Fishers Lane
> Rockville, MD 20857

The expiration dating period for Rozerem (ramelteon) Tablets packaged in bottles of 30, 100, and 500 tablets is 24 months. As discussed during the teleconference on July 20, 2005, you may submit a "Supplement-Changes Being Effected" (CBE-0) for extension of expiration dating following accrual of additional real-time data and statistical analysis as recommended in ICH Q1E.

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Sara Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

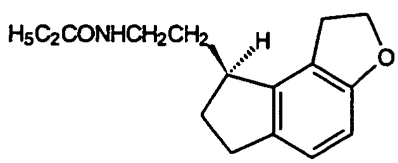
Robert J. Meyer, MD
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Carton Labels
Immediate Container Labels

ROZEREM™
(ramelteon) tablets

DESCRIPTION

ROZEREM™ (ramelteon) is an orally active hypnotic chemically designated as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and containing one chiral center. The compound is produced as the (*S*)-enantiomer, with an empirical formula of $C_{16}H_{21}NO_2$, molecular weight of 259.34, and the following chemical structure:



Ramelteon is freely soluble in organic solvents, such as methanol, ethanol, and dimethyl sulfoxide; soluble in 1-octanol and acetonitrile; and very slightly soluble in water and in aqueous buffers from pH 3 to pH 11.

Each ROZEREM tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

ROZEREM (ramelteon) is a melatonin receptor agonist with both high affinity for melatonin MT_1 and MT_2 receptors and selectivity over the MT_3 receptor. Ramelteon demonstrates full agonist activity *in vitro* in cells expressing human MT_1 or MT_2 receptors, and high selectivity for human MT_1 and MT_2 receptors compared to the MT_3 receptor.

The activity of ramelteon at the MT_1 and MT_2 receptors is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle.

Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates. Ramelteon also does not interfere with the activity of a number of selected enzymes in a standard panel.

The major metabolite of ramelteon, M-II, is active and has approximately one tenth and one fifth the binding affinity of the parent molecule for the human MT_1 and MT_2 receptors, respectively, and is 17 – 25-fold less potent than ramelteon in *in vitro* functional assays. Although the potency of M-II at MT_1 and MT_2 receptors is lower than the parent drug, M-II circulates at higher concentrations than the parent producing 20 – 100 fold greater mean systemic exposure when compared to ramelteon. M-II has weak affinity for the serotonin $5\text{-}HT_{2B}$ receptor, but no appreciable affinity for other receptors or enzymes. Similar to ramelteon, M-II does not interfere with the activity of a number of endogenous enzymes

All other known metabolites of ramelteon are inactive.

Pharmacokinetics

The pharmacokinetic profile of ROZEREM has been evaluated in healthy subjects as well as in subjects with hepatic or renal impairment. When administered orally to humans in doses ranging from 4 to 64 mg, ramelteon undergoes rapid, high first-pass metabolism, and exhibits linear pharmacokinetics. Maximal serum concentration (C_{max}) and area under the concentration-time curve (AUC) data show substantial intersubject variability, consistent with the high first-pass effect; the coefficient of variation for these values is approximately 100%. Several metabolites have been identified in human serum and urine.

Absorption

Ramelteon is absorbed rapidly, with median peak concentrations occurring at approximately 0.75 hour (range, 0.5 to 1.5 hours) after fasted oral administration. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability is only 1.8% due to extensive first-pass metabolism.

Distribution

In vitro protein binding of ramelteon is approximately 82% in human serum, independent of concentration. Binding to albumin accounts for most of that binding, since 70% of the drug is bound in human serum albumin. Ramelteon is not distributed selectively to red blood cells.

Ramelteon has a mean volume of distribution after intravenous administration of 73.6 L, suggesting substantial tissue distribution.

Metabolism

Metabolism of ramelteon consists primarily of oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

The rank order of the principal metabolites by prevalence in human serum is M-II, M-IV, M-I, and M-III. These metabolites are formed rapidly and exhibit a monophasic decline and rapid elimination. The overall mean systemic exposure of M-II is approximately 20- to 100 -fold higher than parent drug.

Elimination

Following oral administration of radiolabeled ramelteon, 84% of total radioactivity was excreted in urine and approximately 4% in feces, resulting in a mean recovery of 88%. Less than 0.1% of the dose was excreted in urine and feces as the parent compound. Elimination was essentially complete by 96 hours post-dose.

Repeated once daily dosing with ROZEREM does not result in significant accumulation owing to the short elimination half-life of ramelteon (on average, approximately 1- 2.6 hours).

The half-life of M-II is 2 to 5 hours and independent of dose. Serum concentrations of the parent drug and its metabolites in humans are at or below the lower limits of quantitation within 24 hours.

Effect of Food

When administered with a high-fat meal, the $AUC_{0\text{-inf}}$ for a single 16-mg dose of ROZEREM was 31% higher and the C_{max} was 22% lower than when given in a fasted state. Median T_{max} was delayed by approximately 45 minutes when ROZEREM was administered with food. Effects of food on the AUC values for M-II were similar. It is therefore recommended that ROZEREM not be taken with or immediately after a high fat meal (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Age: In a group of 24 elderly subjects aged 63 to 79 years administered with a single ROZEREM 16-mg dose, the mean C_{max} and $AUC_{0\text{-inf}}$ values were 11.6 ng/mL (SD, 13.8) and 18.7 ng·hr/mL (SD, 19.4), respectively. The elimination half-life was 2.6 hour (SD, 1.1). Compared with younger adults, the total exposure ($AUC_{0\text{-inf}}$) and C_{max} of ramelteon were 97% and 86% higher, respectively, in elderly subjects. The $AUC_{0\text{-inf}}$ and C_{max} of M-II were increased by 30% and 13%, respectively, in elderly subjects.

Gender: There are no clinically meaningful gender-related differences in the pharmacokinetics of ROZEREM or its metabolites.

Hepatic Impairment: Exposure to ROZEREM was increased almost 4-fold in subjects with mild hepatic impairment after 7 days of dosing with 16 mg/day; exposure was further increased (more than 10-fold) in subjects with moderate hepatic impairment. Exposure to M-II was only marginally increased in mildly and moderately impaired subjects relative to healthy

matched controls. The pharmacokinetics of ROZEREM have not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C). ROZEREM should be used with caution in patients with moderate hepatic impairment (see **WARNINGS**).

Renal Impairment: The pharmacokinetic characteristics of ROZEREM were studied after administering a 16-mg dose to subjects with mild, moderate, or severe renal impairment based on pre-dose creatinine clearance (53 to 95, 35 to 49, or 15 to 30 mL/min/1.73 m^2, respectively), and in subjects who required chronic hemodialysis. Wide inter-subject variability was seen in ROZEREM exposure parameters. However, no effects on C_{max} or AUC_{0-t} of parent drug or M-II were seen in any of the treatment groups; the incidence of adverse events was similar across groups. These results are consistent with the negligible renal clearance of ramelteon, which is principally eliminated via hepatic metabolism. No adjustment of ROZEREM dosage is required in patients with renal impairment, including patients with severe renal impairment (creatinine clearance of $\leq$ 30 mL/min/1.73 m^2) and patients who require chronic hemodialysis.

Chronic Obstructive Pulmonary Disease: The effects of ROZEREM were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate chronic obstructive pulmonary disease. Treatment with ROZEREM 16 mg for one night showed no difference compared with placebo on mean arterial oxygen saturation during sleep for the entire night, for each stage of sleep, or for each hour of sleep, and no significant difference in the Apnea/Hypopnea index. While ROZEREM did not show a respiratory depressant effect in this study of patients with chronic obstructive pulmonary disease, the effect of ROZEREM in patients with severe COPD (e.g., those with elevated pCO_2 levels or those needing nocturnal oxygen therapy) has not been studied.

Sleep Apnea: The effects of ROZEREM were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate obstructive sleep apnea. Treatment with ROZEREM 16 mg for one night showed no difference compared with placebo on the Apnea/Hypopnea Index (the primary outcome variable), apnea index, hypopnea index, central apnea index, mixed apnea index, and obstructive apnea index. Mean SaO_2 during the REM stage of sleep was statistically significantly higher for ROZEREM than for placebo. No differences from placebo were detected in all other secondary outcome variables. These results indicate that ROZEREM does not exacerbate mild to moderate obstructive sleep apnea. ROZEREM has not been studied in subjects with severe obstructive sleep apnea; use of ROZEREM is not recommended in such patients.

Results of drug-drug interaction trials are discussed under **PRECAUTIONS.**

CLINICAL TRIALS

Controlled Trials Supporting Efficacy

Chronic Insomnia

ROZEREM was studied in two randomized, double-blind trials in subjects with chronic insomnia employing polysomnography (PSG).

One study enrolled younger adults (aged 18 to 64 years, inclusive) with chronic insomnia and employed a parallel design in which the subjects received a single, nightly dose of ROZEREM 8 mg or 16 mg or matching placebo for 35 days. PSG was performed on the first two nights in each of Weeks 1, 3, and 5 of treatment. Both doses of ROZEREM reduced the average latency to persistent sleep at each of the time points when compared to placebo.

The second study employing PSG was a three-period crossover trial performed in subjects aged 65 years and older with a history of chronic insomnia. Subjects received ROZEREM 4 mg or 8 mg or placebo and underwent PSG assessment in a sleep laboratory for two consecutive nights in each of the three study periods. Both doses of ROZEREM reduced latency to persistent sleep compared to placebo.

A randomized, double-blind, parallel group study was conducted in outpatients aged 65 years and older with chronic insomnia and employed subjective measures of efficacy (sleep diaries). Subjects received ROZEREM 4 mg or 8 mg or placebo for 35 nights. Both doses of ROZEREM reduced patient-reported sleep latency compared to placebo. A similarly designed study performed in younger adults (aged 18-64 years) using 8 and 16mg of ramelteon did not replicate this finding of reduced patient-reported sleep latency compared to placebo.

Transient Insomnia

In a randomized, double-blind, parallel-group trial using a first-night-effect model, healthy adults received placebo or ROZEREM 8 mg or 16 mg before spending one night in a sleep laboratory and being evaluated with PSG. The 8-mg dose demonstrated a decrease in mean latency to persistent sleep as compared to placebo.

Studies Pertinent to Safety Concerns for Sleep-Promoting Agents

Results from Human Laboratory Abuse Liability Studies

A human laboratory abuse potential study was performed in 14 subjects with a history of sedative/hypnotic or anxiolytic drug abuse. Subjects received single oral doses of ROZEREM (16, 80, or 160mg,), triazolam (0.25, 0.50, or 0.75mg,) or placebo. All subjects received each of the 7 treatments separated by a wash-out period and underwent multiple standard tests of abuse potential. No differences in subjective responses indicative of abuse potential were found between ROZEREM and placebo at doses up to 20 times the recommended therapeutic dose. The positive control drug, triazolam, consistently showed a dose-response effect on these subjective measures, as demonstrated by the differences from placebo in peak effect and overall 24-hour effect.

Residual Pharmacological Effects in Insomnia Trials

In order to evaluate potential next-day residual effects, the following scales were used: a Memory Recall Test, a Word List Memory Test, a Visual Analog Mood and Feeling Scale, the Digit-Symbol Substitution Test, and a post-sleep questionnaire to assess alertness and ability to concentrate.

There was no evidence of next-day residual effect seen after 2 nights of ramelteon use during the crossover studies.

In a 35-night, double-blind, placebo-controlled, parallel-group study in adults with chronic insomnia, measures of residual effects were performed at three time points. Overall, the magnitudes of any observed differences were small. At Week 1, patients who received 8 mg of ROZEREM had a mean VAS score (46 mm on a 100 mm scale) indicating more fatigue in comparison to patients who received placebo (42 mm). At Week 3, patients who received 8 mg of ROZEREM had a lower mean score for immediate recall (7.5 out of 16 words) compared to patients who received placebo (8.2 words); and the ROZEREM-treated patients had a mean VAS score indicating more sluggishness (27 mm on a 100 mm VAS) in comparison to the placebo-treated patients (22 mm). Neither ROZEREM dose had next-morning residual effects that were different from placebo at Week 5.

Rebound Insomnia/Withdrawal

Potential rebound insomnia and withdrawal effects were assessed in three long-term insomnia studies in which subjects received ROZEREM for 35 days. These studies included a total of 2082 subjects, of whom 829 were elderly.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ): The BWSQ is a self-report questionnaire that solicits specific information on 20 symptoms commonly experienced during withdrawal from benzodiazepine receptor agonists. In two of the three 35-day insomnia studies, the questionnaire was administered one week after completion of treatment; in the third study, the questionnaire was administered on Days 1 and 2 after completion.

In all three studies, subjects receiving ROZEREM 4 mg, 8 mg, or 16 mg daily reported BWSQ scores similar to those of subjects receiving placebo.

Rebound Insomnia: Rebound insomnia was assessed in three of the long-term studies by continuing to measure sleep latency after abrupt treatment discontinuation. One of these was studies employed PSG in younger adult subjects receiving ROZEREM 8 mg or 16 mg; the other two studies employed subjective measures of sleep-onset insomnia in elderly subjects receiving ROZEREM 4 mg or 8 mg, and in younger adult subjects receiving ROZEREM 8 mg or 16 mg. In each of these studies, there was no evidence that ROZEREM caused rebound insomnia at any time during the post-treatment period at any of the three doses.

Special Studies to Evaluate Effects on Endocrine Function

Two controlled studies evaluated the effects of ROZEREM on endocrine function.

In the first trial, ROZEREM 16 mg once daily or placebo was administered to 99 healthy volunteer subjects for 4 weeks. This study evaluated the thyroid axis, adrenal axis and reproductive axis. No clinically significant endocrinopathies were demonstrated in this study. However, the study was limited in its ability to detect such abnormalities due to its limited duration.

In the second trial, ROZEREM 16 mg once daily or placebo was administered to 122 subjects with chronic insomnia for 6 months. This study evaluated the thyroid axis, adrenal axis and reproductive axis. There were no significant abnormalities seen in either the thyroid or the adrenal axes. Abnormalities were, however, noted within the reproductive axis. Overall, the mean serum prolactin level change from baseline was 4.9 μg/L (34 % increase) for women in the ROZEREM group compared with -0.6 μg/L (4% decrease) for women in the placebo group ($p=0.003$). No differences between active- and placebo-treated groups occurred among men. Thirty-two percent of all patients who were treated with ramelteon in this study (women and men) had prolactin levels which increased from normal baseline levels compared to nineteen percent of patients who were treated with placebo. Subject-reported menstrual patterns were similar between the two treatment groups.

In a 12-month, open-label study in adult and elderly patients, there were two patients who were noted to have abnormal morning cortisol levels, and subsequent abnormal ACTH stimulation tests. A 29 year old female patient was also diagnosed with a prolactinoma. The relationship of these events to ROZEREM therapy is not clear.

INDICATIONS AND USAGE

ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS

ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS

General

ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children

ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans. (see **Pediatric Use**)

Information for Patients

- Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.
- Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.
- Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.
- Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.
- Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests

No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels, and testosterone levels should be considered as appropriate.

Drug Interactions

ROZEREM has a highly variable inter-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM™ Metabolism

Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the $AUC_{0\text{-}inf}$ for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (See Warnings). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both $AUC_{0\text{-}inf}$ and C_{max}) after a single 32mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The $AUC_{0\text{-}inf}$ and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16mg dose of ROZEREM was administered on the fourth day of ketoconazole 200mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) of ramelteon after a single 16mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM™ on Metabolism of Other Drugs

Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem™

Alcohol: With single-dose, daytime co-administration of ROZEREM 32mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions

ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, $B6C3F_1$ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma $TK^{+/-}$ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m^2 basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m^2 basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m^2 basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m^2 basis) when considering all studies.

Pregnancy: Pregnancy Category C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m^2 basis).

Labor and Delivery

The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers

Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use

A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS

Overview

The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment

Five percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials

Table 1 displays the incidence of adverse events during the Phase 1 through 3 trials.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Table 1. Incidence (% of subjects) of Treatment-Emergent Adverse Events in Phase 1-3 Studies

MedDRA Preferred Term	Placebo (n=1370)	Ramelteon 8 mg (n=1250)
Headache NOS	7%	7%
Somnolence	3%	5%
Fatigue	2%	4%
Dizziness	3%	5%
Nausea	2%	3%
Insomnia exacerbated	2%	3%
Upper respiratory tract infection NOS	2%	3%
Diarrhea NOS	2%	2%
Myalgia	1%	2%
Depression	1%	2%
Dysgeusia	1%	2%
Arthralgia	1%	2%
Influenza	0	1%
Blood Cortisol Decreased	0	1%

DRUG ABUSE AND DEPENDENCE

ROZEREM is not a controlled substance.

Human Data. See **the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents**, for the results of human laboratory abuse potential trials with ROZEREM.

Animal Data. Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotorod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE

Signs and Symptoms

No cases of ROZEREM overdose have been reported during clinical development.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdosage is not appropriate.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of ROZEREM™ is 8 mg taken within 30 minutes of going to bed. It is recommended that ROZEREM not be taken with or immediately after a high fat meal.

ROZEREM should not be used in subjects with severe hepatic impairment. ROZEREM should be used with caution in patients with moderate hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine. ROZEREM should be used with caution in patients taking other CYP1A2 inhibiting drugs (see **PRECAUTIONS: Drug Interactions**).

HOW SUPPLIED

ROZEREM is available as round, pale orange-yellow, film-coated, 8 mg tablets, with "TAK" and "RAM-8" printed on one side, in the following quantities:

NDC 64764-805-30	Bottle of 30
NDC 64764-805-10	Bottle of 100
NDC 64764-805-50	Bottle of 500

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature]. Keep container tightly closed and protected from moisture and humidity.

Rx only

Manufactured by:
Takeda Pharmaceutical Company, Ltd.
540-8645 Osaka, Japan

Manufactured in:
Takeda Ireland Ltd.
Kilruddery, County Wicklow, Republic of Ireland

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Rozerem™ 8 mg Sample Carton

Rozerem™
(ramelteon tablets)
8 mg

For complete prescribing information, please visit www.rozerem.com.

Store at 25°C (77°F); excursions 15°–30°C (59°–86°F).

Protect from moisture and humidity.

Keep out of reach of children.

Each film-coated tablet contains 8 mg of ramelteon.

See bottom panel for lot number and expiration date.

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Marketed by:
Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

FPO 09-1114

Rozerem™ (ramelteon tablets) 8 mg

Professional Sample—Not for Sale
NDC 64764-805-37

Rozerem™
(ramelteon tablets)

8 mg

Contains 1 patient sample of 3 tablets

Takeda

Rx Only

Lot:

Exp.:

FPO 09-1114

DRAFT COPY	DIE LINE	VARNISH	PMS 185C	PMS 3435C	PMS 130C

FINAL PROOF Date: 7/22/2005

Rozerem™ 8 mg Sample Carton	Size: 2.00" X .703" X 3.4375" (50.8 mm X 17.86 mm X 87.31 mm)
Item No.: 09-1114 — P/N.:	Takeda
☐ New Proof Required — ☐ OK With Changes	COMMERCIAL QA OPERATIONS

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg Sample Tray		Size: 4.875" x 3.5625" x 2.09375" (123.83 mm x 90.49 mm x 53.18 mm)
Item No.: 12-1117	P/N.:	Takeda COMMERCIAL QA OPERATIONS
☐ New Proof Required	☐ OK With Changes	

DRAFT COPY | DIE LINE | VARNISH | PMS 186C | PMS 3435C | PMS 130C

Contains 6 patient sample units of 3 tablets each
NDC 64764-805-37
Rozerem™
(ramelteon tablets)
8 mg

Contains 6 patient sample units of 3 tablets each
NDC 64764-805-37
Rozerem™
(ramelteon tablets)
8 mg

See package insert for complete prescribing information.
Store at 25°C (77°F); excursions 15°-30°C (59°-86°F).
Protect from moisture and humidity.
Keep out of reach of children.
Each film-coated tablet contains 8 mg of ramelteon.

Rozerem™ is a trademark of
Takeda Pharmaceutical Company Limited
and used under license by
Takeda Pharmaceuticals America, Inc.

Contains 6 patient sample units of 3 tablets each
Professional Sample – Not for Sale
Rozerem™
(ramelteon tablets)
8 mg
Rx Only
Takeda

See package insert for complete prescribing information.
Store at 25°C (77°F); excursions 15°-30°C (59°-86°F).
Protect from moisture and humidity.
Keep out of reach of children.
Each film-coated tablet contains 8 mg of ramelteon.

04/05 Printed in U.S.A. 12-1117

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN
Marketed by:
Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

Lot
Exp.

FPO
12-1117

Rozerem™ 8 mg/500 Count Label

FPO

3 64764-805-50 0

07-1118

Store at 25°C (77°F), excursions 15°-30°C (59°-86°F)
Protect from moisture and humidity
Keep container tightly closed
©2005 Takeda Pharmaceuticals America, Inc.

NDC 64764-805-50
500 Tablets

Rozerem™

(ramelteon tablets)

8 mg

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Marketed by:
Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

Rx Only

Do not accept if seal imprinted with "SEALED for YOUR PROTECTION" over bottle opening is broken or missing

Each film-coated tablet contains 8 mg of ramelteon.

Dispense in a USP tight, light-resistant container

See package insert for complete prescribing information.

Keep out of reach of children

™ - Trademark

Lot

Exp.:

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/500 Count		Size: 4.00" x 1.75" (101.6 mm x 44.45 mm)
Item No.: 07-1118	P/N.:	Takeda COMMERCIAL QA OPERATIONS
☐ New Proof Required	☐ OK With Changes	

DIE LINE | VARNISH | BLACK | PMS 185C | PMS 3435C | PMS 130C

Rozerem™ 8 mg/100 Count Label

FPO

N 3 64764-805-10 4

07-1115

Store at 25°C (77°F), excursions 15-30°C (59°-86°F).
Protect from moisture and humidity.
Keep container tightly closed.
©2005 Takeda Pharmaceuticals America, Inc

NDC 64764-805-10
100 Tablets

Rozerem™

(ramelteon tablets)

8 mg

Manufactured by
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Marketed by
Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

Takeda

Rx Only

Do not accept if seal imprinted with "SEALED for YOUR PROTECTION" over bottle opening is broken or missing.

Each film-coated tablet contains 8 mg of ramelteon

Dispense in a USP tight, light-resistant container

See package insert for complete prescribing information.

Keep out of reach of children

™ - Trademark

Lot

Exp.

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/100 Count		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1115	P/N.:	Takeda COMMERCIAL QA OPERATIONS
☐ New Proof Required	☐ OK With Changes	

DIE LINE | VARNISH | BLACK | PMS 185C | PMS 130C | PMS 3435C

Rozerem ™ 8 mg/30 Count Label

FPO

3 64764-805-30 1

07-1112

Store at 25°C (77°F), excursions 15°-30°C (59°-86°F).
Protect from moisture and humidity.
Keep container tightly closed.
©2005 Takeda Pharmaceuticals America, Inc

NDC 64764-805-30
30 Tablets

Rozerem™

(ramelteon tablets)

8 mg

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Marketed by:
Takeda Pharmaceuticals America, Inc
Lincolnshire, IL 60069

Rx Only

Do not accept if seal imprinted with "SEALED for YOUR PROTECTION" over bottle opening is broken or missing.

Each film-coated tablet contains 8 mg of ramelteon

Dispense in a USP tight, light-resistant container

See package insert for complete prescribing information.

Keep out of reach of children.

™ - Trademark

Lot:

Exp.

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/30 Count		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1112	P/N.:	Takeda COMMERCIAL QA OPERATIONS
☐ New Proof Required	☐ OK With Changes	

DIE LINE | VARNISH | BLACK | PMS 185C | PMS 3435C | PMS 130C

Rozerem™ 8 mg/30 Count Sample Label

FPO

3 64764-805-33 3

07-1148

Store at 25°C (77°F); excursions 15°-30°C (59°-86°F).
Protect from moisture and humidity.
Keep container tightly closed.
© 2005 Takeda Pharmaceuticals America, Inc.

NDC 64764-805-33
30 Tablets

Rozerem™

(ramelteon tablets)

8 mg

Manufactured by
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Marketed by
Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

Takeda

Rx Only

Professional Sample - Not for Sale

Do not accept if seal imprinted with "SEALED for YOUR PROTECTION" over bottle opening is broken or missing.

Each film-coated tablet contains 8 mg of ramelteon.

See package insert for complete prescribing information.

Keep out of reach of children

™ Trademark

Lot

Exp.:

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/30 Count Sample Label		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1148	P/N.:	Takeda COMMERCIAL QA OPERATIONS
☐ New Proof Required	☐ OK With Changes	

DIE LINE | VARNISH | BLACK | PMS 185C | PMS 3435C | PMS 130C

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
7/22/05 04:31:23 PM

EXHIBIT E.

A copy of United States Patent No. 6,034,239.

US006034239A

United States Patent [19]

Ohkawa et al.

[11] **Patent Number: 6,034,239**

[45] **Date of Patent: Mar. 7, 2000**

[54] **TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE**

[75] Inventors: **Shigenori Ohkawa**, Osaka; **Osamu Uchikawa**, Hyogo; **Kohji Fukatsu**, Hyogo; **Masaomi Miyamoto**, Hyogo, all of Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.**, Osaka, Japan

[21] Appl. No.: **08/812,168**

[22] Filed: **Mar. 6, 1997**

Related U.S. Application Data

[60] Provisional application No. 60/013,733, Mar. 20, 1996, and provisional application No. 60/023,090, Jul. 25, 1996.

[30] **Foreign Application Priority Data**

Mar. 8, 1996	[JP]	Japan	8-051491
Jul. 12, 1996	[JP]	Japan	8-183667
Feb. 13, 1997	[JP]	Japan	9-029185

[51] **Int. Cl.**^{7} **C07D 413/00**; C07D 493/00; C07D 307/92; C07C 233/00

[52] **U.S. Cl.** **544/147**; 544/153; 549/387; 549/458; 564/189

[58] **Field of Search** 564/189; 544/387, 544/458, 153, 147

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,296,482	3/1994	Peglion et al.	514/213
5,552,418	9/1996	Depreux et al.	514/348
5,661,186	8/1997	Takaki et al.	514/630

FOREIGN PATENT DOCUMENTS

0420064	4/1991	European Pat. Off.	C07C 233/23
0527687	2/1993	European Pat. Off.	C07D 209/16
0708099	4/1996	European Pat. Off.	
WO 17405	6/1995	WIPO.	
WO 29173	11/1995	WIPO.	
WO 95-35320	12/1995	WIPO.	

OTHER PUBLICATIONS

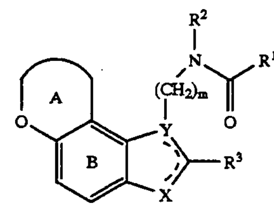
Macor et al., J. Med. Chem., vol. 35, No. 20 (1992) 3625–32.

Tetrahedron Letters, vol. 36, No. 39 (1995) 7019–7022.

Primary Examiner—John Kight
Assistant Examiner—Raymond Covington
Attorney, Agent, or Firm—Fitzpatrick, Cella, Harper & Scinto

[57] **ABSTRACT**

A compound of the formula:



wherein R^1 is an optionally substituted hydrocarbon, amino or heterocyclic group; R^2 is H or an optionally substituted hydrocarbon group; R^3 is H or an optionally substituted hydrocarbon or heterocyclic group; X is CHR^4, NR^4, O or S in which R^4 is H or an optionally substituted hydrocarbon group; Y is C, CH or N; ring A is optionally substituted 5- to 7-membered ring; ring B is an optionally substituted benzene ring; and m is 1 to 4, or a salt thereof, a process for producing it, an intermediate for the production and a pharmaceutical composition comprising it are provided.

41 Claims, No Drawings

TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE

This application claims priority of provisional application 60/013,733, filed Mar. 20, 1996 and provisional application 60/023,090, filed Jul. 25, 1996.

TECHNICAL FIELD

The present invention relates to a tricyclic compound with excellent binding affinity for melatonin receptor, a process for producing and use thereof.

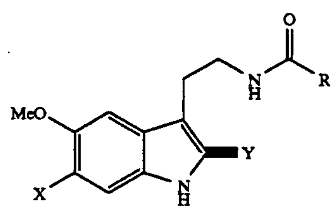
BACKGROUND ART

Melatonin (N-acetyl-5-methoxytryptamine), which is a hormone synthesized and secreted principally in the pineal gland, increases in dark circumstances and decreases in light circumstances. Melatonin exerts suppressively on pigment cells and the female gonads, and acts as a synchronous factor of biological clock while taking part in transmittance of photoperiodic code. Therefore, melatonin is expected to be used for the therapy of diseases related with melatonin activity, such as reproduction and endocrinic disorders, sleep-awake rhythm disorders, jet-lag syndrome and various disorders related to aging, etc.

Recently, it has been reported that the production of melatonin melatonin could reset the body's aging clock (see Ann. N. Y. Acad. Sci., Vol. 719, pp. 456–460 (1994)). As previously reported, however, melatonin is easily metabolized by metabolic enzymes in vivo (see Clinical Examinations, Vol. 38, No. 11, pp. 282–284 (1994)). Therefore, it cannot be said that melatonin is suitable as a pharmaceutical substance.

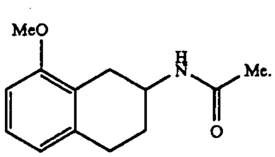
Various melatonin agonists and antagonists such as those mentioned below are known.

(1) EP-A-578620 discloses compounds of:

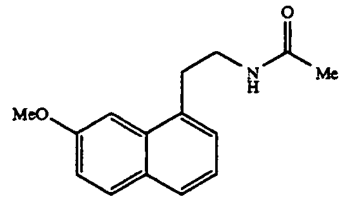


X = H, Y = Br, R = Me
X = H, Y = I, R = Me
X = Cl, Y = H, R = Me
X = H, Y = CH_3, R = cyclopropyl.

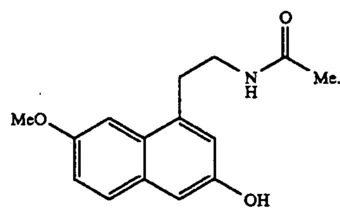
(2) EP-A-420064 U.S. Pat. No. 5,634,238 discloses a compound of:



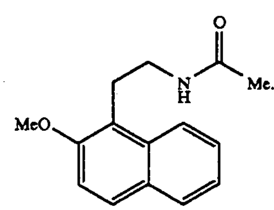
(3) EP-A-447285 discloses a compound of:



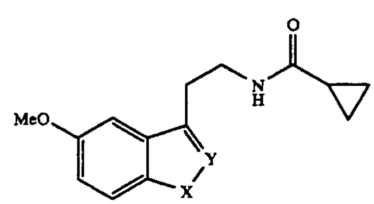
(4) U.S. Pat. No. 5,552,418 (FR-93 14630) discloses a compound of:



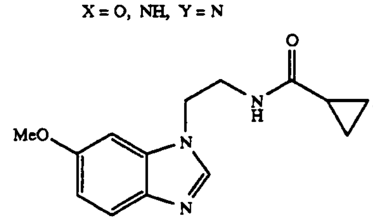
(5) EP-A-591057 discloses a compound of:



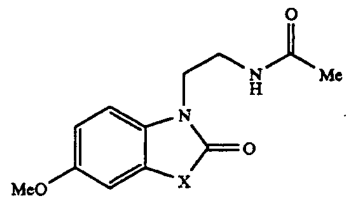
(6) EP-A-527687 discloses compounds of:



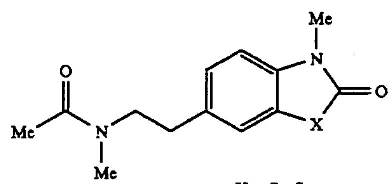
X = S, O, Y = CH
X = O, NH, Y = N



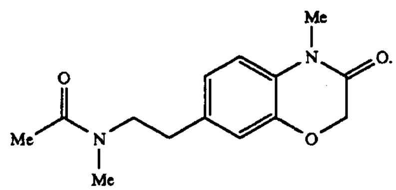
(7) EP-A-506539 discloses compounds of:



X = O, S

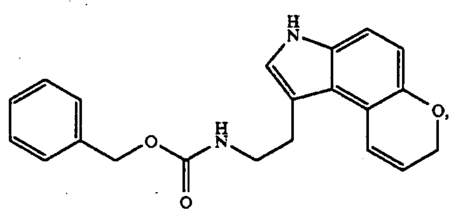


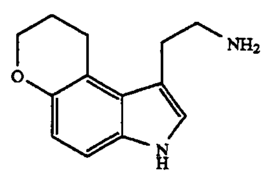
X = O, S



Tricyclic or more poly-cyclic compounds with a cyclic ether moiety, such as those mentioned below, are known.

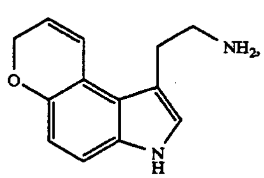
(1) Compounds of:

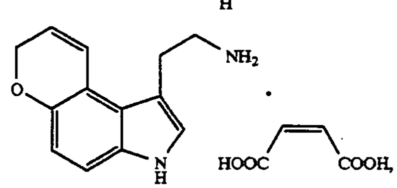




are disclosed in Tetrahedron Lett., Vol. 36, p. 7019 (1995).

(2) Compounds of:





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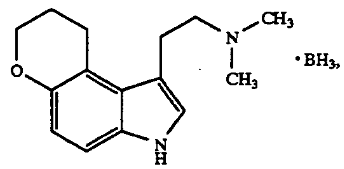
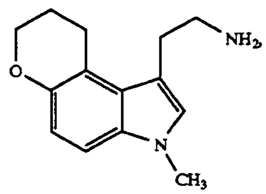
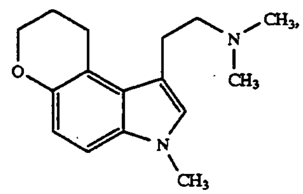
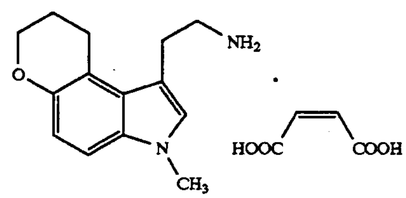


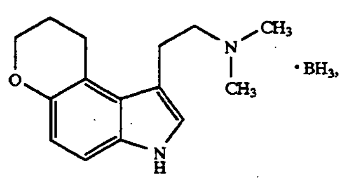


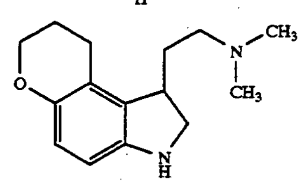




are disclosed in J. Med. Chem., Vol. 35, p. 3625 (1992).

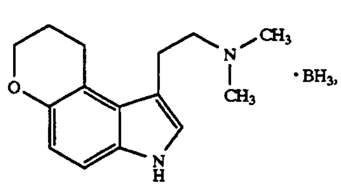
(3) Compounds of:





are disclosed in Tetrahedron, Vol. 48, p. 1039 (1992).

(4) Compounds of:



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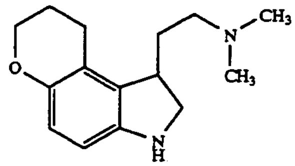
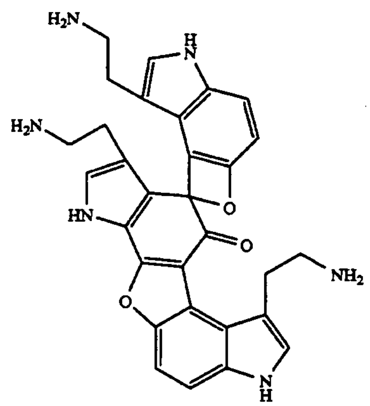


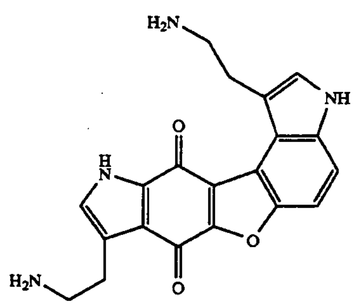
are disclosed in Tetrahedron Lett., Vol. 32, p. 3345 (1991).

(5) A compound of:



is disclosed in Bioorg. Chem., Vol. 18, p. 291 (1990).

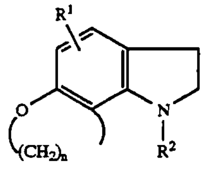
(6) A compound of:



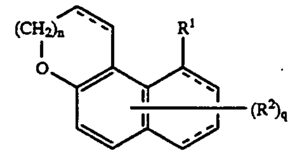
is disclosed in J. Electroanal. Chem. Interfacial Electrochem., Vol. 278, p. 249 (1990).

However, there is no report referring to the relationship between these compounds and melatonin receptors.

As tricyclic compounds with an affinity for melatonin receptor, known are compounds of:



wherein R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group; R^2 represents —$CR^3R^4(CH_2)_pNR^5COR^6$ (in which R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_{1-6} alkyl group, and R^6 represents a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group); n represents an integer of 2 to 4; and p represents an integer of from 1 to 4 (WO-A-9517405), and compounds of:



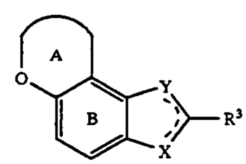
wherein R^1 represents —$CR^3R^4(CH_2)_pNR^5COR^6$ (in which R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_{1-6} alkyl group, and R^6 represents a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group); R^2 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, OR^7 or CO_2R^7 (in which R^7 represents a hydrogen atom or a C_{1-6} alkyl group), provided that when q is 2, each of R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, OR^7 or CO_2R^7; n represents an integer of 0 to 2; p represents an integer of 1 to 4; and q represents 1 or 2 (WO-A-9529173).

Melatonin agonists having different structures from that of melatonin and having an excellent binding affinity for melatonin receptor, excellent intracerebral mobility and excellent metabolical stability are expected to be more effective as a pharmaceutical remedy than melatonin.

At present, no compounds are known which are fully satisfactory with respect to their activity on melatonin receptor, and to their metabolical stability and the intracerebral mobility. Therefore, it is earnestly desired to develop compounds which are different from the above-mentioned known compounds in terms of their chemical structure, which have excellent agonistic or antagonistic activity towards melatonin receptor and which are therefore fully satisfactory for use in medicines such as pharmaceutical preparations.

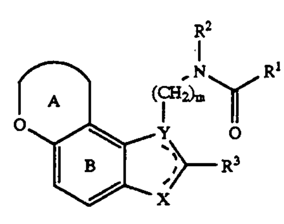
SUMMARY OF THE INVENTION

The present invention relates to a novel compound which is characterized in having a R^1—CO-amino-C_{1-4} alkylene group (in which R^1 is of the same meanings as defined hereinafter) at Y of the basic skeleton moiety of the formula:



wherein all symbols are of the same meanings as defined hereinafter and is represented by the formula:

(I)



wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;

R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group;

R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y represents C, CH or N, provided that when X is CH_2, Y is C or CH;

$\overline{.........}$ represents a single bond or a double bond;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring; and

m represents an integer of 1 to 4, or a salt thereof, or a salt thereof [hereinafter referred to as compound (I)], which has an unexpected good binding affinity for melatonin receptor as a melatonin agonist and is therefore sufficiently satisfactory for use in medicines such as pharmaceutical preparations.

DETAILED EXPLANATION OF THE INVENTION

The present invention provides;

(1) the compound (I),

(2) the compound of the above (1), wherein R^1 is

(i) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkylcarbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino,

(ii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, or

(iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11} aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^2 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

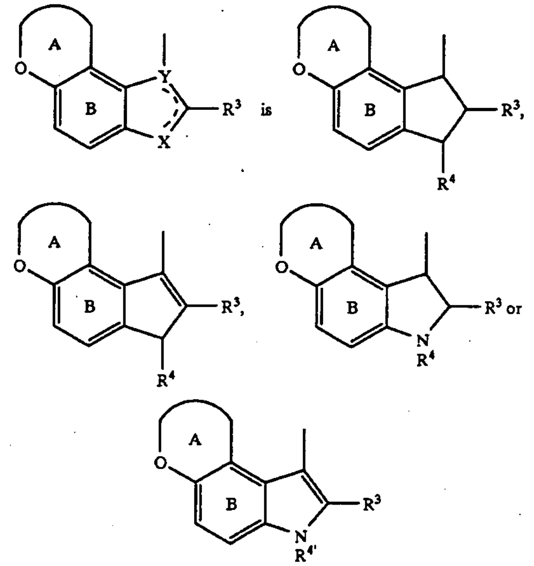
R^3 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11} aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^4 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

ring A is a 5- to 7-membered heterocyclic group optionally containing, besides carbon atoms and an oxygen atom, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 4 substituents selected from the group consisting of (i) a C_{1-6} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (ii) a halogen, (iii) C_{1-6} alkoxy, (iv) C_{6-10} aryloxy, (v) formyl, (vi) C_{1-6} alkyl-carbonyl, (vii) C_{6-10} aryl-carbonyl, (viii) formyloxy, (ix) C_{1-6} alkyl-carbonyloxy, (x) C_{6-10} aryl-carbonyloxy, (xi) carboxyl, (xii) C_{1-6} alkoxy-carbonyl, (xiii) C_{7-11} aralkyloxy-carbonyl, (xiv) carbamoyl, (xv) an optionally halogenated C_{1-4} alkyl, (xvi) oxo, (xvii) amidino, (xviii) imino, (xix) amino, (xx) mono-C_{1-4} alkylamino, (xxi) di-C_{1-4} alkylamino, (xxii) 3- to 6-membered cyclic amino, (xxiii) C_{1-3} alkylenedioxy, (xxiv) hydroxy, (xxv) nitro, (xxvi) cyano, (xxvii) mercapto, (xxviii) sulfo, (xxix) sulfino, (xxx) phosphono, (xxxi) sulfamoyl, (xxxii) mono-C_{1-6} alkylsulfamoyl, (xxxiii) di-C_{1-6} alkylsulfamoyl, (xxxiv) C_{1-6} alkylthio, (xxxv) C_{6-10} arylthio, (xxxvi) C_{1-6} alkylsulfinyl, (xxxvii) C_{6-10} arylsulfinyl, (xxxviii) C_{1-6} alkylsulfonyl and (xxxix) C_{6-10} arylsulfonyl; and ring B is a benzene ring which may be substituted by 1 or 2 substituents selected from the group consisting of (i) a halogen, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (iii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (iv) a C_{1-6} alkanoylamino group, (v) a C_{1-6} alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (vi) a C_{1-3} alkylenedioxy group,

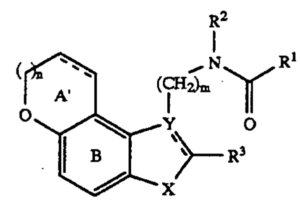
(3) the compound of the above (1), wherein



wherein $R^{4'}$ is an optionally substituted hydrocarbon group and the other symbols are as defined above,

(4) the compound of the above (1), which is a compound of the formula:

(II)



wherein ring A' is an optionally substituted, oxygen-containing heterocyclic ring;

n is an integer of 0 to 2;

---- and .... are the same or different and each is a single bond or a double bond;

and the other symbols are as defined above,

(5) the compound of the above (1), wherein R^1 is (i) an optionally substituted C_{1-6} alkyl group, (ii) an optionally substituted C_{3-6} cycloalkyl group, (iii) an optionally substituted C_{2-6} alkenyl group, (iv) an optionally substituted C_{6-14} aryl group, (v) an optionally substituted mono- or di-C_{1-6} alkylamino group, (vi) an optionally substituted C_{6-14} arylamino group, or (vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group,

(6) the compound of the above (1), wherein R^1 is an optionally halogenated C_{1-6} alkyl group,

(7) the compound of the above (1), wherein R^2 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

(8) the compound of the above (1), wherein R^2 is a hydrogen atom,

(9) the compound of the above (1), wherein R^3 is a hydrogen atom or an optionally substituted hydrocarbon group,

(10) the compound of the above (1), wherein R^3 is a hydrogen atom,

(11) the compound of the above (1), wherein R^4 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

(12) the compound of the above (1), wherein X is CHR^4,

(13) the compound of the above (1), wherein X is CHR^4 and .... is a single bond,

(14) the compound of the above (13), wherein X is CH_2,

(15) the compound of the above (1), wherein X is NR^4,

(16) the compound of the above (1), wherein Y is C or CH,

(17) the compound of the above (1), wherein Y is CH,

(18) the compound of the above (1), wherein m is 2,

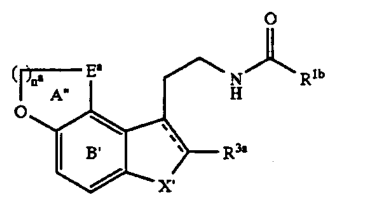
(19) the compound of the above (1), wherein ring A is a tetrahydrofuran ring,

(20) the compound of the above (1), wherein ring A is unsubstituted,

(21) the compound of the above (1), wherein ring B is unsubstituted,

(22) the compound of the above (4), wherein n is 0 or 1,

(23) the compound of the above (1) which is a compound of the formula:



wherein R^{1b} is C_{1-6} alkyl,
X' is CH_2, NH or NCHO,
.... is a single bond or double bond,
R^{3a} is a hydrogen atom or a phenyl,
E^a is CH_2CH_2, CH=CH, CH_2O, CH=N, CONH or CH_2NH,
n^a is 0 or 1,
ring A" is a 5- or 6-membered oxgen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and
ring B' is a benzene ring which may be substituted by a halogen,

(24) the compound of the above (23), wherein .... is single bond and X' is NH,

(25) the compound of the above (1), which is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl] propionamide,

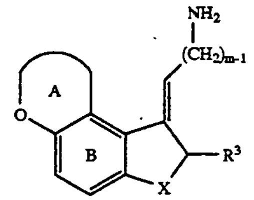
(26) the compound of the above (1), which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl] propionamide,

(27) the compound of the above (1), which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl] butyramide,

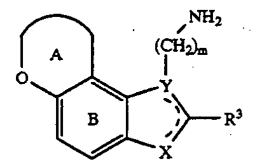
(28) the compound of the above (1), which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl] propionamide,

(29) the compound of the above (1), which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl] butyramide,

(30) a process for producing a compound of the above (1), which comprises reacting a compound of the formula (i):



wherein all symbols are as defined in the above (1), or (ii):

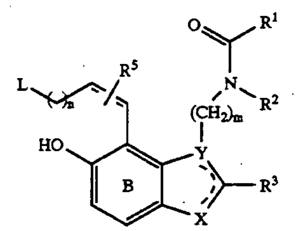


wherein all symbols are as defined above, or a salt thereof, with a compound of the formula:

R^1COOH

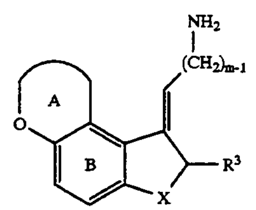
wherein R^1 is as defined above, or a salt thereof or a reactive derivative thereof, if necessary, subjecting the resultant compound to reduction and/or alkylation,

(31) a process for producing a compound of the above (4), which comprises subjecting a compound of the formula:



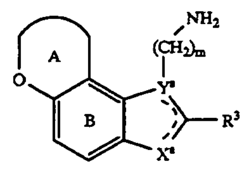
wherein R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxy group, a nitro group, a cyano group or an optionally substituted amino group; L represents a leaving group; and the other symbols are as defined above, or a salt thereof to cyclization, and if necessary, subjecting the resultant compound to reduction,

(32) a compound of the formula:



wherein the symbols are as defined above, or a salt thereof,

(33) a compound of the formula:



wherein X represents CHR^{4a}, NR^{4a}, O or S in which R^{4a} represents a hydrogen atom or an optionally substituted hydrocarbon group; Y^a represents C, CH or N, provided that when X^a is NH, Y^a is CH or N; and the other symbols are as defined above, or a salt thereof,

(34) a pharmaceutical composition which comprises the compound of the above (1),

(35) the composition of the above (34) which has a binding affinity for melatonin receptor,

(36) the composition of the above (35) which is a regulating agent of circadian rhythm,

(37) the composition of the above (35) which is a regulating agent of sleep-awake rhythm,

(38) the composition of the above (35) which is a regulating agent of time zone change syndrome, and

(39) the composition of the above (35) which is a therapeutic agent of sleep disorders.

The "hydrocarbon group" in "optionally substituted hydrocarbon group" as referred to herein includes, for example, an aliphatic hydrocarbon group, a mono-cyclic saturated hydrocarbon group, an aromatic hydrocarbon group, etc., and this preferably has from 1 to 16 carbon atoms. Concretely, this includes, for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group, etc.

The "alkyl group" is, for example, preferably a lower alkyl group and generally includes C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl group" is, for example, preferably a lower alkenyl group and generally includes C_{2-6} alkenyl groups such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, etc.

The "alkynyl group" is, for example, preferably a lower alkynyl group and generally includes C_{2-6} alkynyl groups such as ethynyl, propargyl, 1-propynyl, etc.

The "cycloalkyl group" is, for example, preferably a lower cycloalkyl group and generally includes C_{3-6} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "aryl group" is preferably a C_{6-14} aryl group, including, for example, phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl, etc. Of these, phenyl is generally used.

The substituents for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a hydroxy group, an optionally halogenated lower alkyl group (e.g., an optionally halogenated C_{1-6} alkyl group such as methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a lower alkoxy group (e.g., a C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, etc.), an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-6} alkylamino group such as methylamino, ethylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-6} lower alkylamino group such as dimethylamino, diethylamino, etc.), a carboxyl group, a lower alkylcarbonyl group (e.g., a C_{1-6} alkyl-carbonyl group such as acetyl, propionyl, etc.), a lower alkoxycarbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkylcarbamoyl group (e.g., a mono-C_{1-6} alkyl-carbamoyl group such as methylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkylcarbamoyl group (e.g., a di-C_{1-6} alkyl-carbamoyl group such as dimethylcarbamoyl, diethylcarbamoyl, etc.), an arylcarbamoyl group (e.g., a C_{6-10} aryl-carbamoyl group such as phenylcarbamoyl, naphthylcarbamoyl, etc.), an aryl group (e.g., a C_{6-10} aryl group such as phenyl, naphthyl, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group such as phenyloxy, naphthyloxy, etc.), an optionally halogenated lower alkylcarbonylamino group (e.g., an optionally halogenated C_{1-6} alkylcarbonylamino group such as acetylamino, trifluoroacetylamino, etc.), an oxo group, etc. The "hydrocarbon group" of the "optionally substituted hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents selected from those mentioned above, at any substitutable positions in the group. When the number of the substituents is two or more, each of the substituents may be the same or different.

The "heterocyclic group" in "optionally substituted heterocyclic group" as referred to herein includes, for example, a 5- to 14-membered (preferably, 5- to 10-membered), mono- to tri-cyclic (preferably mono- or di-cyclic) heterocyclic group, each having 1 or 2 kinds, 1 to 4 (preferably 1 to 3) hetero atoms selected from nitrogen, oxygen and sulfur, in addition to carbon atoms. Concretely, it includes, for example, a 5-membered heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, in addition to carbon atoms, such as 2- or 3-thienyl, 2-or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 3- or 4-pyrazolidinyl, 2-, 4-, or 5-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl; a 6-membered heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms, such as 2-, 3- or 4-pyridyl, N-oxido-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido-2-, 4- or 5-pyrimidinyl, thiomorpholinyl, morpholinyl, piperidino, 2-, 3- or 4-piperidyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl; a di- or tricyclic condensed heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms (preferably, a group to be formed by condensing the above-mentioned 5- or 6-membered cyclic group with one or two 5- or 6-membered cyclic groups each optionally having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms), such as indolyl, benzofuryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-naphthyridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, chromanyl, phenothiazinyl, phenoxazinyl, etc. Of these, preferred are 5- to 7-membered (preferably, 5- or 6-membered) heterocyclic groups each having 1 to 3

hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms.

The substituents for the "heterocyclic group" of the "optionally substituted heterocyclic group" include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a lower alkynyl group (e.g., a C_{2-6} alkynyl group such as ethynyl, 1-propynyl, propargyl, etc.), a lower alkenyl group (e.g., a C_{2-6} alkenyl group such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, etc.), an aralkyl group (e.g., a C_{7-11} aralkyl group such as benzyl, α-methylbenzyl, phenethyl, etc.), an aryl group (e.g., a C_{6-10} aryl group such as phenyl, naphthyl, etc., preferably phenyl), a lower alkoxy group (e.g., a C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group such as phenoxy, etc.), a lower alkanoyl group (e.g., formyl, a C_{1-6} alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C_{6-10} aryl-carbonyl group such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., formyloxy, a C_{1-6} alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C_{6-10} arylcarbonyloxy group such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-11} aralkyloxycarbonyl group such as benzyloxycarbonyl, etc.), a carbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C_{1-4} alkyl group such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-4} alkylamino group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-4} alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, etc.), a 3- to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3- to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), a hydroxy group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfino group, a phosphono group, a sulfamoyl group, a monoalkylsulfamoyl group (e.g., a mono-C_{1-6} alkylsulfamoyl group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C_{1-6} alkylsulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., C_{1-6} alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C_{6-10} arylthio group such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C_{1-6} alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C_{6-10} arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C_{1-6} alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C_{6-10} arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The "heterocyclic group" of the "optionally substituted heterocyclic group" may have 1 to 5, preferably 1 to 3 substituents selected from those mentioned above, at any substitutable positions in the group. In the case that the group has two or more substituents, these substituents may be the same or different.

The "optionally substituted amino group" as referred to herein includes amino groups each optionally having one or two substituents of, for example, the above-mentioned "optionally substituted hydrocarbon groups". Preferred substituents for the above "amino group" include, for example, an optionally substituted C_{1-6} alkyl group and an optionally substituted C_{6-10} aryl group. The substituents which the "C_{1-6} alkyl group" or the "C_{6-10} aryl group" may optionally have are, for example, the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "lower alkyl group" for "optionally substituted lower alkyl group" as referred to herein includes, for example, a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The lower alkyl group may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "lower alkoxy group" in "optionally substituted lower alkoxy group" as referred to herein includes, for example, a C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy. The lower alkoxy group may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "optionally substituted benzene ring" as referred to herein includes, for example, a benzene ring which may optionally have one or two substituents selected from, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), an optionally substituted hydrocarbon group, an optionally substituted amino group, an amido group (e.g., a C_{1-3} acylamino group such as formamido, acetamido, etc.), an optionally substituted lower alkoxy group and a lower alkylenedioxy group (e.g., a C_{1-3}alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), at any substitutable positions in the ring.

For these "optionally substituted hydrocarbon group", "optionally substituted amino group" and "optionally substituted lower alkoxy group", the same ones as those described in detail hereinabove are referred to. In the case that these "hydrocarbon group", "amino group" and "lower alkoxy group" each have two or more substituents, these substituents may be the same or different.

The "optionally substituted benzene ring" is preferably a benzene ring optionally substituted by 1 or 2 substituents selected from a halogen atom (e.g., fluorine, chlorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl, etc.) and a mono-C_{1-6} alkylamino group.

In the above-mentioned formulae, R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^1 is preferably, for

example, an alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g., C_{2-6} alkenyl group such as vinyl, etc.), an alkynyl group (e.g., a C_{2-6} alkynyl group such as ethynyl), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or an aryl group (e.g., a C_{6-14} aryl group such as phenyl, etc.), especially preferably an alkyl group (e.g., a C_{1-6} alkyl group such as methyl, etc.) or a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group such as cyclopropyl, etc.). These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may have 1 to 5, preferably 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have, preferably halogen atoms such as fluorines.

Preferred substituents for the "optionally substituted amino group" represented by R^1, are one or two substituents selected from, for example, an optionally substituted lower alkyl group and an optionally substituted aryl group, more preferably one substituent of an optionally substituted lower alkyl group. The "lower alkyl group" includes, for example, a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The "lower alkyl group" may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have. The "aryl group" includes, for example, a C_{6-10} aryl group such as phenyl, etc. The "aryl group" may optionally have 1 to 5, preferably 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have, preferably those selected from, for example, a halogen atom such as fluorine and chlorine and a C_{1-6} alkoxy group such as methoxy and ethoxy. The "optionally substituted amino group" includes, for example, a phenylamino group substituted by, 1 to 3 lower alkoxy groups (e.g., C_{1-4} alkoxy groups such as methoxy, etc.) or a monoalkylamino group substituted by one lower alkyl group (e.g., a C_{1-4} alkyl group such as methyl, ethyl, propyl, butyl, tert-butyl, etc.)

The "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R^1 is, for example, preferably a 5- or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely, it includes, for example, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl and 3-isoxazolyl. Especially preferably, it is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.).

Preferred substituents for the "optionally substituted heterocyclic group" represented by R^1 include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl, etc.), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy, etc.) and an aralkyloxycarbonyl group (e.g., a C_{7-12} aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.).

R^1 is, for example, preferably (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an optionally substituted arylamino group or (vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group.

The "lower alkyl group" is preferably a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl. The "lower cycloalkyl group" is preferably a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The "lower alkenyl group" is preferably a C_{2-6} alkenyl group such as vinyl, 1-propenyl and butenyl. The "aryl group" is preferably a C_{6-10} aryl group such as phenyl, 1-naphthyl and 2-naphthyl. The "lower alkylamino group" is preferably a mono- or di-C_{1-6} alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, dimethylamino, diethylamino and methylethylamino. The "arylamino group" is preferably a C_{6-10} arylamino group such as phenylamino. The "5- or 6-membered nitrogen-containing heterocyclic group" is, for example, preferably 2-, 3- or 4-pyridyl or the like. These groups may each optionally have 1 to 5 substituents such as those referred to the mentioned-above "hydrocarbon group" may optionally have.

More preferably, R^1 is (i) a C_{1-6} alkyl group optionally substituted by 1 to 4 substituents selected from a halogen atom and a C_{1-6} alkoxy group, (ii) a C_{3-6} cycloalkyl group, (iii) a C_{2-6} alkenyl group, (iv) a C_{6-10} aryl group optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkoxy group, a nitro group, a halogeno-C_{1-6} alkyl-carbonylamino group and a halogen atom, (v) a mono- or di-C_{1-6} alkylamino group, (vi) a C_{6-10} arylamino group optionally substituted by one to three C_{1-6} alkoxy groups, or (vii) a 6-membered nitrogen-containing heterocyclic group optionally substituted by one or two C_{7-11} aralkyloxycarbonyl groups. Even more preferably, R^1 is an optionally halogenated C_{1-6} alkyl group (e.g., methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) or a mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, etc.) Among ohters, R^1 is preferably an optionally halogenated C_{1-6} alkyl group or a mono-C_{1-6} alkylamino group, especially an optionally halogenated C_{1-6} alkyl, in particular C_{1-3} alkyl group (e.g., methyl, ethyl, propyl, etc.).

In the above-mentioned formulae, R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group.

R^2 is preferably a hydrogen atom or an optionally substituted lower (C_{1-6}) alkyl group, more preferably a hydrogen atom or a lower (C_{1-6}) alkyl group, even more preferably a hydrogen atom.

In the above-mentioned formulae, R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group or optionally substituted heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^3 is preferably, for example, an alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g., a C_{2-6} alkenyl group such as vinyl, etc.), an alkynyl group (e.g., a C_{2-6} alkynyl group such as ethynyl, etc.), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) or an aryl group (e.g., a C_{6-14} aryl group such as phenyl, etc.). It is more preferably an alkyl group (e.g., a C_{1-6} alkyl group such as methyl, etc.) or an aryl group (e.g., a C_{6-14} aryl groups such as phenyl, etc.). These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may optionally have 1 to 5, preferably 1 to 3 substituents such as the same ones the mentioned-above

"hydrocarbon group" may optionally have (e.g., halogen atoms such as fluorines, etc.).

The "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R^3 is preferably a 5- or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms, in addition to carbon atoms. Concretely, it includes, for example, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, etc. More preferred is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.).

Preferred substituents for the "optionally substituted heterocyclic group" represented by R^3 include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl, etc.), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-12} aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.), an amino group, a mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, etc.) a di-C_{1-6} alkylamino group (e.g., dimethylamino, diethylamino, etc.) etc.

R^3 is, for example, preferably (i) a hydrogen atom, (ii) an optionally substituted lower alkyl group, (iii) an optionally substituted aryl group, (iv) an optionally substituted 5- or 6-membered heterocyclic group, etc., more preferably, for example, (i) a hydrogen atom, (ii) a lower alkyl group, (iii) an optionally substituted C_{6-10} aryl group, (iv) an optionally substituted 6-membered nitrogen-containing heterocyclic group.

The above substituents include, for example, a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, an amino group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, etc.

More preferably, R^3 is, for example, a hydrogen atom, a phenyl group and a 2-, 3- or 4-pyridyl group, especially preferably is a hydrogen atom.

In the above-mentioned formulae, X represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group.

X^a represents CHR^{4a}, NR^{4a}, O or S in which R^{4a} represents a hydrogen atom or an optionally substituted hydrocarbon group.

R^4 and R^{4a} are preferably a hydrogen atom or an optionally substituted lower (C_{1-6}) alkyl group, respectively. More preferred is a hydrogen atom.

X is preferably CHR^4 in which R^4 is as defined above, O or S. Or, X is preferably CHR^4 or NR^4 in which R^4 is as defined above.

X^a is preferably CHR^{4a} or NR^{4a} in which R^{4a} is as defined above.

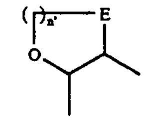
In the above formulae, Y represents C, CH or N. Y is preferably C or CH.

Y^a represents C, CH or N. Y^a is preferably C or CH.

In the above-mentioned formulae, ring A or ring A' represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring.

The "5- to 7-membered oxygen-containing heterocyclic ring" includes 5- to 7-membered (preferably 5- or 6-membered) heterocyclic rings optionally having 1 or 2 kinds, 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms, in addition to carbon atoms and an oxygen atom.

The above-mentioned heterocyclic ring is preferably a ring represented by the formula:

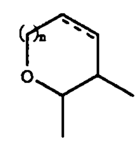


wherein E represents (i) CH_2CH_2, (ii) CH=CH, (iii) CH_2O, (iv) OCH_2, (v) $CH_2S(O)_{q'}$, wherein q' represents an integer of 0 to 2, (vi) $S(O)_{q'}CH_2$ wherein q' is as defined above, (vii) CH_2NH, (viii) $NHCH_2$, (ix) N=N, (x) CH=N, (xi) N=CH or (xii) CONH; and n' represents an integer of 0 to 2.

E is preferably (i) CH_2CH_2, (ii) CH=CH, (iii) CH_2O, (iv) OCH_2, (v) CH_2NH, (vi) $NHCH_2$, (vii) N=N, (viii) CH=N or (ix) N=CH, especially preferably (i) CH_2CH_2 or (ii) CH=CH.

Concretely, the above ring includes, for example, a 5-membered oxygen-containing heterocyclic ring such as 2,3-dihydrofuran, furan, 1,3-dioxole, oxazoline, isoxazole, 1,2,3-oxadiazole and oxazole and a 6-membered oxygen-containing heterocyclic ring such as 2H-3,4-dihydropyran, 2H-pyran, 2,3-dehydro-1,4-dioxane and 2,3-dehydromorpholine.

More preferably, the above ring is a ring represented by the formula:



wherein n is as defined above.

Concretely, 2,3-dihydrofuran, furan, 2H-3,4-dihydropyran and 2H-pyran are preferred.

Substituents which ring A or ring A' may optionally have, include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), an optionally. substituted lower alkyl (e.g., C_{1-6} alkyl) group, an optionally substituted cycloalkyl (e.g., C_{3-6} cycloalkyl) group, an optionally substituted lower alkynyl (e.g., C_{2-6} alkynyl) group, an optionally substituted lower alkenyl (e.g., C_{2-6} alkenyl) group, an optionally substituted aryl (e.g., C_{6-10} aryl) group, a lower alkoxy group (e.g., a C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group such as phenoxy, etc.), a lower alkanoyl group (e.g., formyl, a C_{1-6} alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C_{6-10} aryl-carbonyl group such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., formyloxy, a C_{1-6} alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C_{6-10} arylcarbonyloxy group such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an aralkyloxy group (e.g., a C_{7-11} aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.), a carbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C_{1-4} alkyl group such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-4}

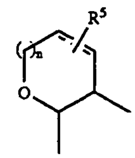
alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-4} alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, etc.), a 3- to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3- to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), a hydroxyl group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfino group, a phosphono group, a sulfamoyl group, a monoalkylsulfamoyl group (e.g., a mono-C_{1-6} alkylsulfamoyl group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C_{1-6} alkylsulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., a C_{1-6} alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C_{6-10} arylthio group such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C_{1-6} alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C_{6-10} arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C_{1-6} alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C_{6-10} arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The above "lower alkyl group", "lower alkenyl group", "lower alkynyl group", "lower cycloalkyl group" and "aryl group" each may optionally have the same ones as the above-mentioned 1 to 5, preferably 1 to 3 substituents such as those "hydrocarbon group" may optionally have.

Preferred substituents which ring A or ring A' may optionally have, include, for example, a halogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{1-6} alkoxy group, a hydroxyl group, a nitro group, a cyano group, an optionally substituted amino group and an oxo group. For the substituents in these "optionally substituted C_{1-6} alkyl group", "optionally substituted C_{1-6} alkoxy group" and "optionally substituted amino group", for example, referred to are the substituents which mentioned-above "hydrocarbon group" may optionally have.

Ring A and ring A' may have 1 to 4, preferably one or two substituents selected from those mentioned above at any substitutable positions, depending on the number of the carbon atoms constituting them. When the ring has two or more substituents, these substituents may be the same or different.

Ring A and ring A' are, for example;



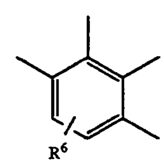
wherein n is as defined above; and R^5 represents a hydrogen atom or 1 or 2 substituents selected from the "preferred substituents for ring A or ring A'" mentioned hereinabove. R^5 is preferably a hydrogen atom and 1 or 2 optionally substituted lower (C_{1-6}) alkyl, more preferably, a hydrogen atom, which indicates unsubstituted ring A and unsubstituted ring A'.

In the above-mentioned formulae, ring B represents an optionally substituted benzene ring.

The substituents which ring B may optionally have, include, for example, the "substituents" mentioned hereinabove for the "optionally substituted benzene ring". Among others, the substituents on ring B are preferably a halogen atom and an optionally substituted lower (C_{1-6}) alkyl group, more preferably a halogen atom and a lower (C_{1-6}) alkyl group (especially, methyl). As for the substituents for the "optionally substituted lower (C_{1-6}) alkyl group", for example, referred to are the same ones as the mentioned-above "hydrocarbon group" may optionally have.

Ring B may have one or two, preferably one substituent selected from those mentioned hereinabove, at any substitutable position. When ring B has two substituents, they may be the same or different.

For example, ring B is preferably

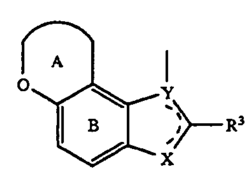


wherein R^6 represents a hydrogen atom, a halogen atom, an optionally substituted lower (C_{1-6}) alkyl group or an optionally substituted lower (C_{1-6}) alkoxy group. R^6 is preferably a hydrogen atom, a halogen atom or a lower (C_{1-6}) alkyl group (especially, methyl). More preferred, R^6 is a hydrogen atom.

In the above-mentioned formulae, m represents an integer of 1 to 4. Preferably, m is an integer of 1 to 3. More preferred is 2 or 3. Especially 2 is preferable.

In the above-mentioned formulae, n represents an integer of 0 to 2. Preferably, n is an integer of 0 or 1. Especially 0 is preferable.

Examples of



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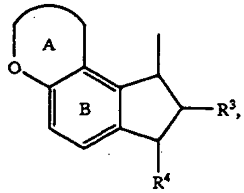
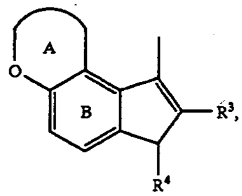
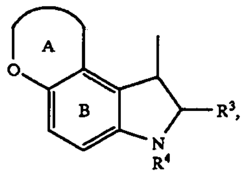
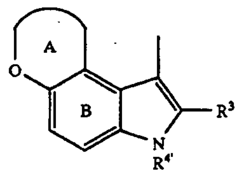




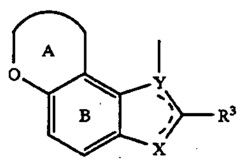




wherein $R^{4'}$ represents an optionally substituted hydrocarbon group and the other symbols are as defined above.

$R^{4'}$ is preferably an optionally substituted lower (C_{1-3}) alkyl group.

Preferred examples of



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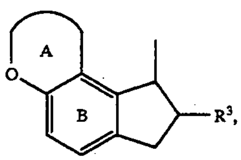
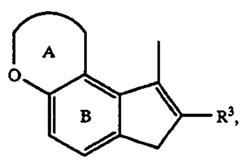
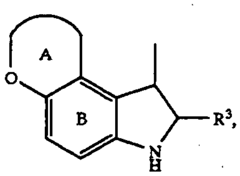
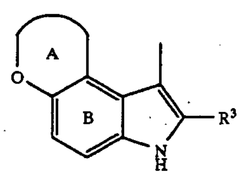
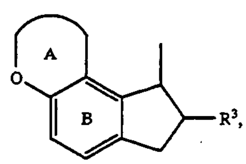


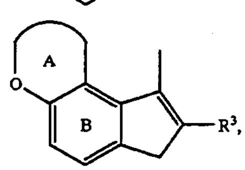






wherein are symbols are as defined above. Among them, preferred are





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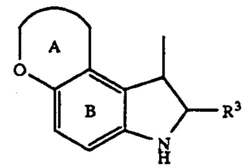
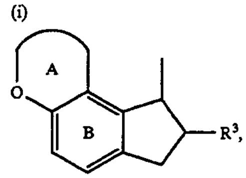
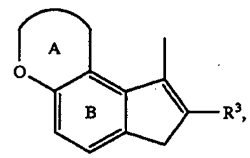


wherein the symbols are as defined above.

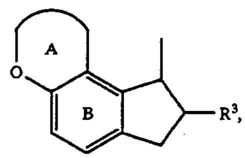
Further preferred are

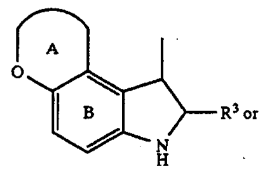
(i)



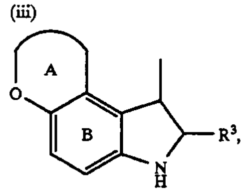


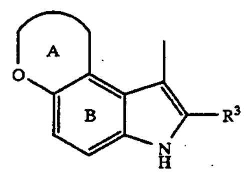
(ii)





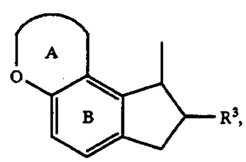
(iii)

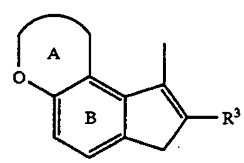




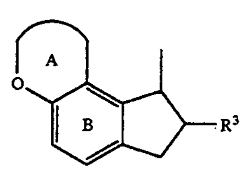
wherein the symbols are as defined above.

More preferred are





wherein the symbols are as defined above. Especially preferred is



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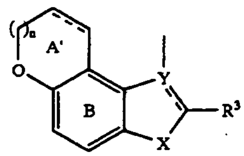
Preferred examples of



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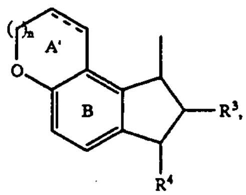
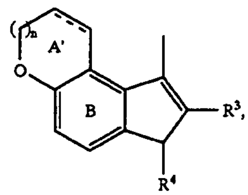
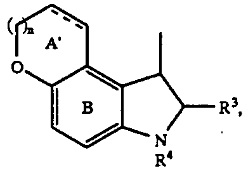
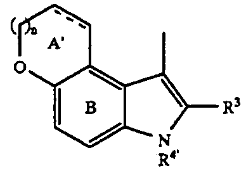


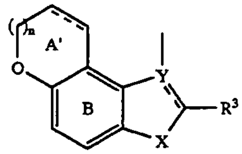






wherein the symbols are as defined above.

Especially preferred examples of



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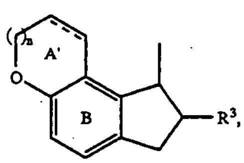
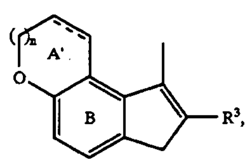
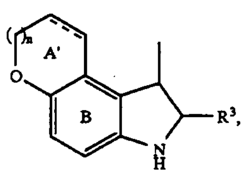
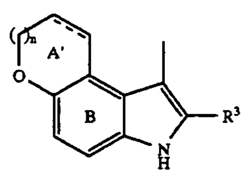


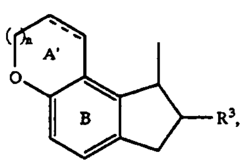


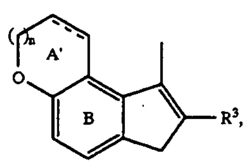




wherein the symbols are as defined above.

Preferred among them are





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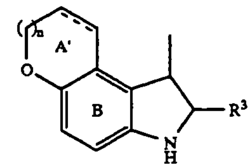
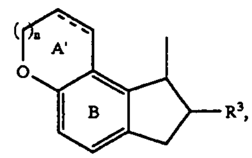
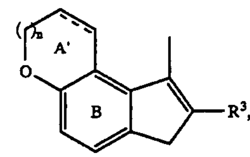


wherein the symbols are as defined above.

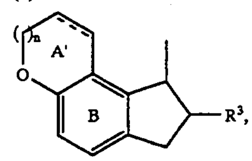
Further preferred are

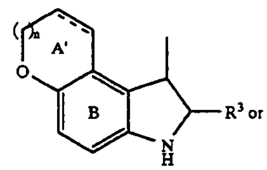
(i)



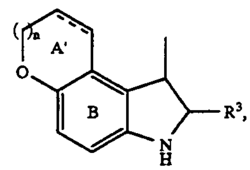


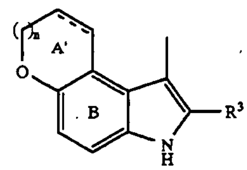
(ii)





(iii)





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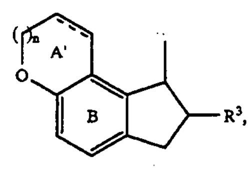
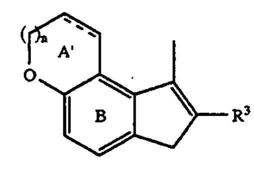
Among them, more preferred are





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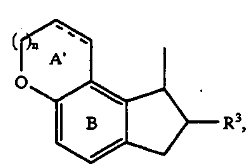
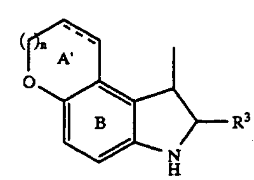
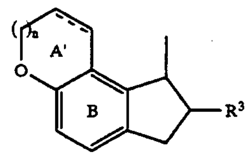
Among them, more preferred are also





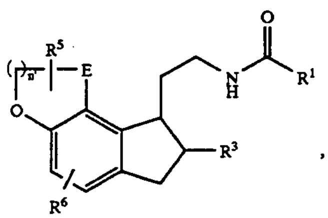
wherein the symbols are as defined above.

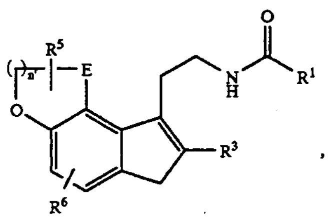
Especially preferred is

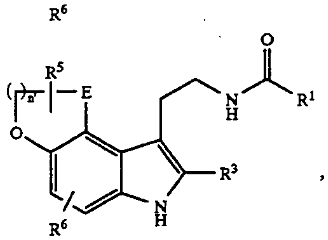


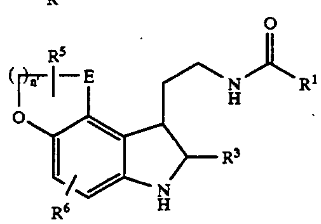
wherein the symbols are as defined above.

Example of the compound (I) of the present invention include compounds having the following structural formulae.



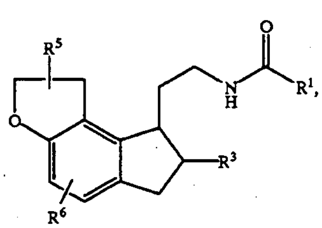






wherein the symbols are as defined above.

Preferred examples of the compound (I) include, for example, compounds of the following formulae:



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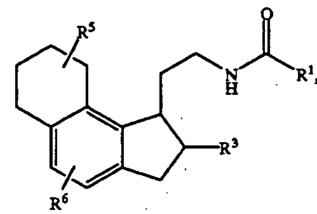
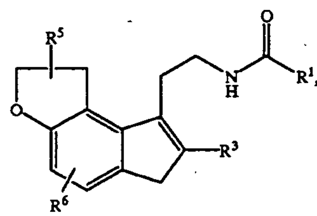
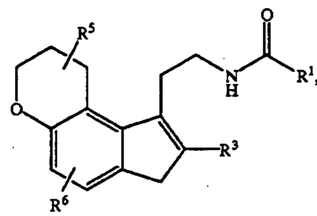
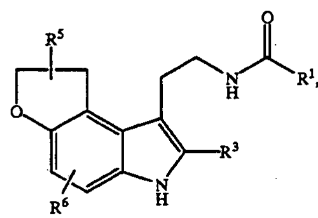
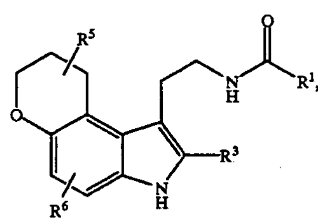
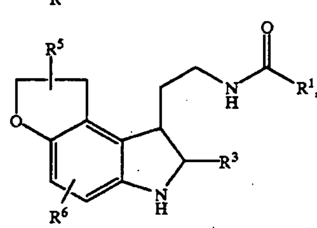


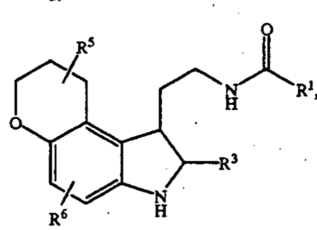












wherein the symbols are as defined above.

Also preferred examples of the compound (I) are the compound of the formula (I) wherein;

R^1 is (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an optionally substituted arylamino group or (vii) an optionally substituted, 5- or 6-membered nitrogen-containing heterocyclic group;

R^2 is a hydrogen atom or an optionally substituted lower (C_{1-6}) alkyl group;

R^3 is (i) a hydrogen atom, (ii) an optionally substituted lower alkyl group or (iii) an optionally substituted aryl group;

X is CHR^4 or NR^4 wherein R^4 is a hydrogen atom or a lower (C_{1-6}) alkyl group optionally substituted by an oxo group;

Y is C, CH or N, provided that when X is CH_2, Y is C or CH;

$\overline{\cdots\cdots}$ is a single bond or a double bond;

ring A is an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B is an optionally substituted benzene ring; and

m is 1 or 2.

More preferred is the compound wherein

R^1 is (i) a C_{1-6} alkyl group optionally substituted by 1 to 4 substituents selected from the group consisting of a halogen and a C_{1-6} alkoxy group, (ii) a C_{3-6} cycloalkyl group, (iii) a C_{2-6} alkenyl group, (iv) a C_{6-10} aryl group optionally substituted by 1 to 4 substituents selected from the group consisting of a C_{1-6} alkoxy group, a nitro group, a halogeno-C_{1-6} alkyl-carbonylamino group and a halogen, (v) a mono- or di-C_{1-6} alkylamino group, (vi) a C_{6-10} arylamino group optionally substituted by 1 to 3 C_{1-6} alkoxy groups or (vii) a 6-membered nitrogen-containing heterocyclic group optionally substituted by one or two C_{7-11} aralkyloxy-carbonyl groups;

R^2 is a hydrogen atom or a lower (C_{1-6}) alkyl group;

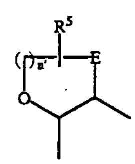
R^3 is (i) a hydrogen atom, (ii) a lower (C_{1-6}) alkyl group or (iii) a C_{6-14} aryl group;

X is CHR^4 or NR^4 wherein R^4 is a hydrogen atom or a lower (C_{1-6}) alkyl group optionally substituted by an oxo group;

Y is C, CH or N, provided that when X is CH_2, Y is C or CH;

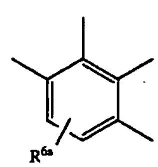
$\overline{\cdots\cdots}$ is a single bond or a double bond;

ring A is



wherein the symbols are as defined above;

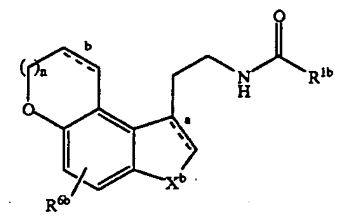
ring B is



wherein R^{6a} represents a hydrogen atom, a halogen atom or a lower (C_{1-6}) alkyl group; and

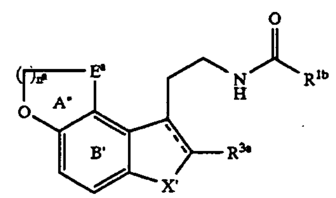
m is 1 or 2.

Preferred among them is the compound represented by the formula:



wherein R^{1b} represents a C_{1-6} alkyl group, R^{6b} represents a hydrogen atom or a halogen atom, n represents 0 or 1, $\overset{b}{\overline{\cdots\cdots}}$ represents a single bond or a doulbe bond, $\overset{a}{\overline{\cdots\cdots}}$ represents a single bond or a double bond when X^b is CH_2, and $\overset{a}{\overline{\cdots\cdots}}$ represents a single bond when X^b is NH, and a salt thereof.

Preferred among them is also the compound by the formula:



wherein R^{1b} is C_{1-6} alkyl, X' is CH_2, NH or NCHO, $\overline{\cdots\cdots}$ is a single bond or double bond, R^{3a} is a hydrogen atom or a phenyl, E^a is CH_2CH_2, CH═CH, CH_2O, CH═N, CONH or CH_2NH, n^a is 0 or 1, ring A" is a 5- or 6-membered oxgen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and ring B' is a benzene ring which may be substituted by a halogen, and a salt thereof. Among them, the compound wherein $\overline{\cdots\cdots}$ is a single bond or double bond when X' is CH_2 or NCHO, and $\overline{\cdots\cdots}$ is a single bond when X' is NH is also preferred.

Preferable examples of the compound (I) include,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

(R)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]propionamide,

N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]butyramide,

N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-yl)ethyl]propionamide,

N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide,

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, and

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

More preferred are

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan- 8-yl)ethyl]propionamide,

N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]-benzopyran-9-yl)ethyl]propionamide,

N-[2-(5-fluoro-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide,

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

(R)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide,

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, and

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

Especially preferred are

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide,

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide,

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, and

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

Salts of the compound (I) of the present invention include, for example, pharmaceutically acceptable salts thereof. For example, mentioned are salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids. Preferred examples of salts with inorganic bases include, for example, alkali metal salts such as sodium salts and potassium salts, alkaline earth metal salts such as calcium salts and magnesium salts, aluminium salts and ammonium salts. Preferred examples of salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferred examples of salts with inorganic acids include, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferred examples of salts with organic acids include, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid. Preferred examples of salts with basic amino acids include, for example, salts with arginine, lysine and ornithine. Preferred examples of salts with acidic amino acids include, for example, salts with aspartic acid and glutamic acid.

Among others, preferred are pharmaceutically acceptable salts which include, for example, salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid or salts with organic acids such as acetic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid and p-toluenesulfonic acid, when the compound (I) has basic functional group(s); and alkali metal salts such as sodium salts and potassium salts, or alkaline earth metal salts such as calcium salts and magnesium salts, and ammonium salts when the compound (I) has acidic functional group(s).

Compound (I) of the present invention may be hydrated or solvated.

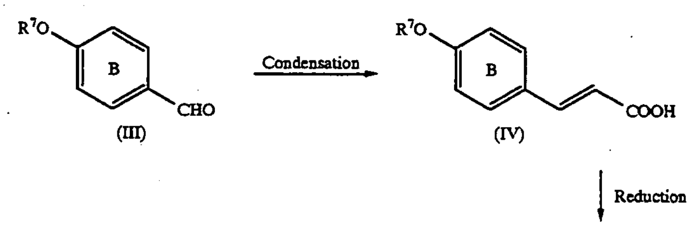
A process for producing the compound (I) and a salt thereof (referred to Compound (I) as hereinunder) of the present invention is mentioned below.

Compound (I) of the present invention can be produced in accordance with, for example, the reaction processes illustrated in the following reaction schemes or the analogous thereto.

Compounds (III) to (LXXIV) in the following reaction schemes encompass their salts, for which the salts of Compound (I) mentioned hereinabove are referred to.

The symbols for the compounds in the following reaction schemes are as defined those mentioned above.

Reaction Process 1:



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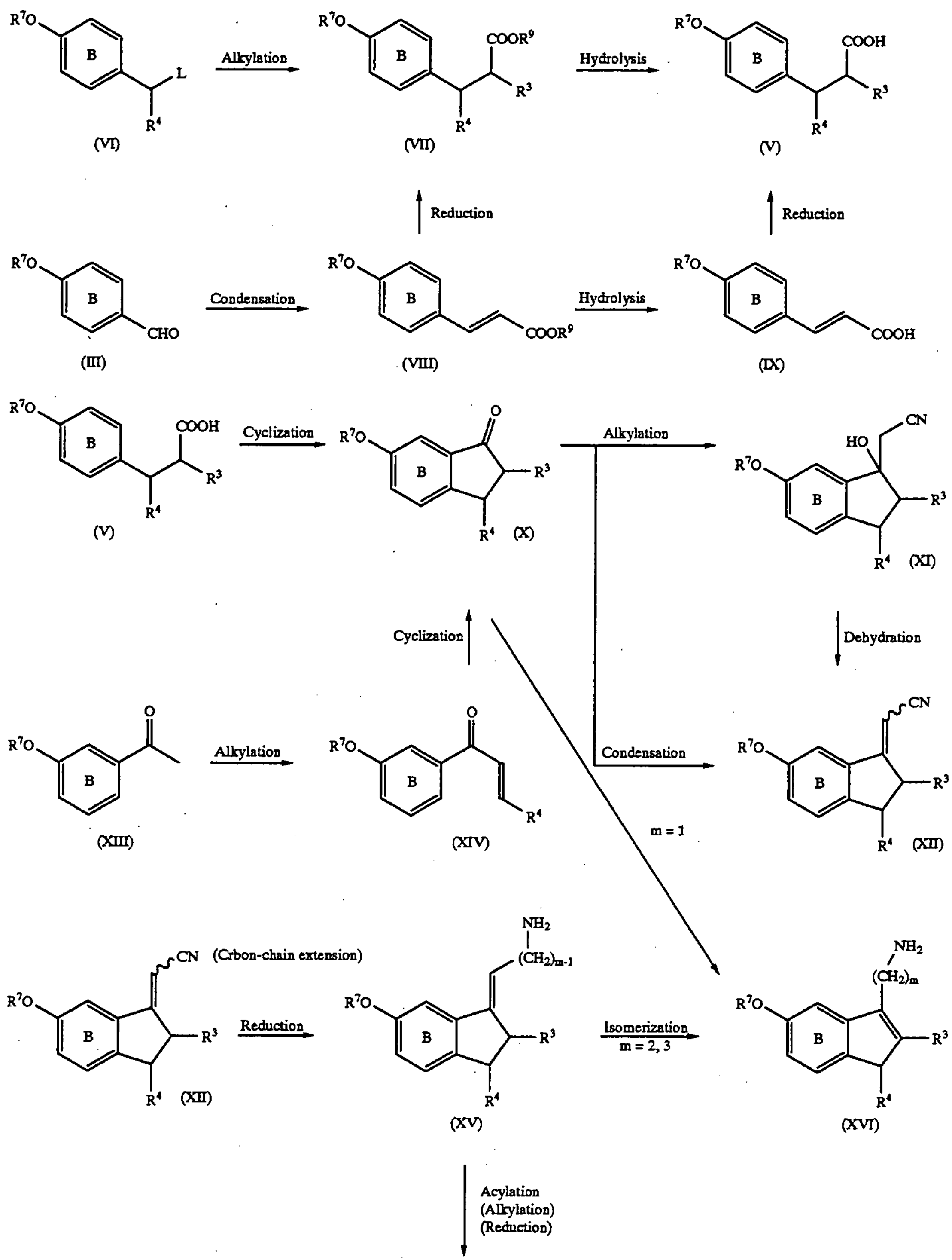
R7O
B
L
R4
(VI)
Alkylation
COOR9
R3
(VII)
Hydrolysis
COOH
(V)
Reduction
CHO
(III)
Condensation
(VIII)
(IX)
Cyclization
(X)
HO
CN
(XI)
Dehydration
(XIII)
(XIV)
Condensation
(XII)
m = 1
NH2
(CH2)m-1
(Crbon-chain extension)
Isomerization
m = 2, 3
(CH2)m
(XV)
(XVI)
Acylation
(Alkylation)
(Reduction)

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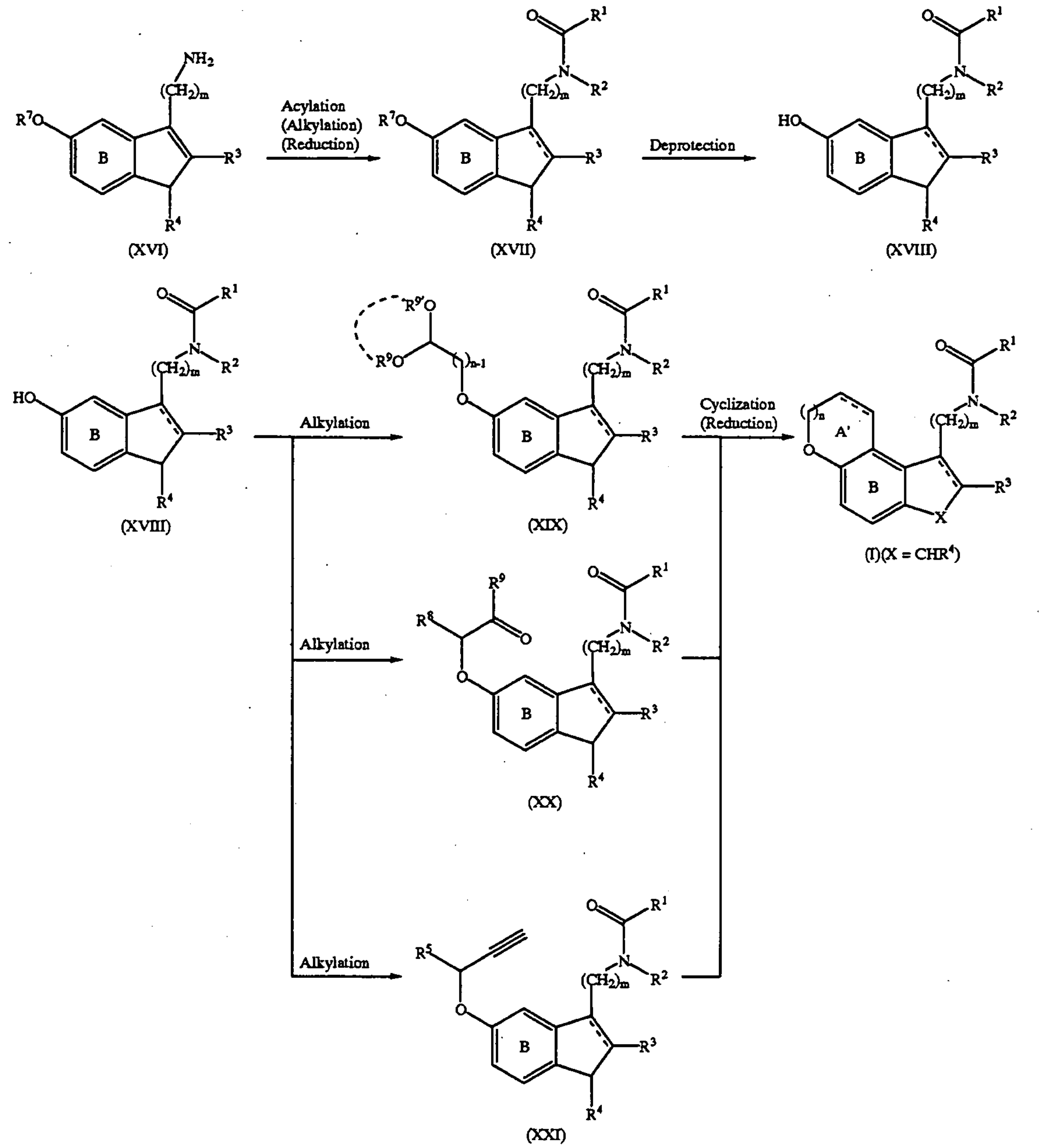


Compound (III) can be produced using per se known methods, for example, using the methods described in Jikken Kagaku Koza (Lectures on Experimental Chemistry), 4th Ed., Vol. 21, pp. 1-148 (edited by the Japan Chemical Society) or methods analogous thereto.

Compound (VI) wherein L represents a leaving group such as a halogen atom, an alkylsulfonyl group, an alkylsulfonyloxy group and an arylsulfonyloxy group, and R^7 represents an optionally substituted hydrocarbon group can be produced using per se known methods, for example, using the methods described in Bull. Chem. Soc. Japan, Vol. 64, p. 1410 (1991), J. Indian Chem. Soc., Vol. 66, p. 656 (1989), J. Med. Chem., Vol. 29, p. 1586 and p. 1904 (1986), or methods analogous thereto.

Compound (XIII) can be produced using per se known methods, for example, using the methods described in J. Chem. Soc., p. 4691 (1963), Chem. Lett., p. 165 (1986) or methods analogous thereto.

The halogen atom represented by L includes, for example, fluorine, chlorine, bromine and iodine. The alkylsulfonyl group represented by L includes, for example, a C_{1-5} alkylsulfonyl group (e.g., methanesulfonyl, ethanesulfonyl, etc.). The alkylsulfonyloxy group represented by L includes, for example, an optionally halogenated C_{1-5} alkylsulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.). The arylsulfonyloxy group represented by L includes, for example, an optionally substituted benzenesulfonyloxy group (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy, etc.).

For the compounds in the above-mentioned reaction schemes, commercial products, if available, can be directly used.

Compound (IV) can be produced from compound (III) and malonic acid through the Knoevenagel condensation thereof in the presence of a base. One mol of compound (III) is reacted with approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols of malonic acid. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of approximately 0.1 to 10.0 mols, preferably approximately 0.1 to 5.0 mol per mol of compound (III). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; or a suitable mixture of these solvents are preferable. The reaction time varies, depending on the reagents and solvents used, and is generally 30 minutes to 24 hours, preferably 30 minutes to 8 hours. The reaction temperature is generally 0 to 150° C., preferably 0 to 130° C. The product (IV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (VIII) (in which R^9 represents a hydrocarbon group) can be obtained by reacting a phosphonato-carbanion, which is produced by the treatment of a trialkyl phosphonoacetate with a base, with compound (III). This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The trialkyl phosphonoacetate includes, for example, triethyl phosphonoacetate, etc. One mol of compound (III) is reacted with approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.5 mols of the trialkyl phosphonoacetate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols, per mol of compound (III). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 1 hour to 50 hours, preferably 1 hour to 10 hours. The reaction temperature is generally −78 to 200° C., preferably 0 to 150° C. The mixture of isomers of compound (VIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (IX) can be produced by hydrolyzing the ester moiety of compound (VIII) with an acid or base. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are inorganic bases such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately 0.5 to 10 mols, preferably approximately 0.5 to 3.0 mols per mol of compound (VIII). The reaction is advantageously conducted either in the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitrites such as acetonitrile, propionitrile, etc.; ketones such as acetone, methylethylketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 60 hours, preferably 10 minutes to 12 hours. The reaction temperature is generally −10 to 200° C., preferably 0 to 120° C. The product (IX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (VII) (in which R^9 represents a hydrocarbon group) can be produced by reacting compound (VI) with an ester derivative of the formula $R^3CH_2COOR^9$ (in which R^3 and R^9 are as defined above) in the presence of a base. For the "hydrocarbon group" represented by R^9, for example, referred to is the above-mentioned "hydrocarbon group". Among others, R^9 is preferably a lower alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, isopropyl, etc.) or an optionally substituted benzyl group. The "optionally substituted benzyl group" may have 1 to 3 substituents such as halogen atoms and C_{1-3} alkyl at any substitutable positions in the benzyl group. Concretely, it includes, for example, benzyl, p-chlorobenzyl, p-methylbenzyl, etc.

The above ester derivative is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (VI). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine,

lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (VI). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally −20 to 200° C., preferably −10 to 150° C. The product (VII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (VII) in which R^3 and R^4 are hydrogens can also be produced by catalytically reducing compound (VIII) in a hydrogen atmosphere in the presence of various catalysts. The catalysts usable for the reduction include, for example, platinum oxide, platinum on activated carbon, palladium on activated carbon, palladium on barium sulfate, nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. The amount of the catalyst to be used may be approximately 5 to 1000% by weight, preferably approximately 5 to 300% by weight relative to compound (VIII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time varies, depending on the activity of the catalyst used and the amount thereof, and is generally 30 minutes to 24 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 120° C., preferably 20 to 80° C. The pressure for the reaction is generally 1 to 100 atmospheres. Additives (promoters) that enhance the activity of the catalyst used can be added to the reaction system. Acidic additives advantageously usable for the purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. The product (VII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (V) in which R^3 and R^4 are hydrogens can be produced by catalytically reducing compound (IV) or compound (IX) in a hydrogen atmosphere in the same manner as in the reduction to produce compound (VII).

Compound (V) can also be produced by hydrolyzing the ester moiety of compound (VII) with an acid or a base. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are inorganic bases such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately 0.5 to 10 mols, preferably approximately 0.5 to 6.0 mols per mol of compound (VII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides suchas N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitrites such as acetonitrile, propionitrile, etc.; ketones such as acetone, methylethylketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 60 hours, preferably 10 minutes to 12 hours. The reaction temperature is generally −10 to 200° C., preferably 0 to 120° C. The product (V) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XIV) can be produced from compound (XIII) and an aldehyde derivative of the formula R^4CHO (in which R^4 is as defined above), through aldol condensation in the presence of a base. This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The aldehyde derivative is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine,

4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. These bases are used in an amount of approximately 1.0 to 5.0 mols, preferably 1.0 to 2.5 mols per mol of compound (XIII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitrites such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally −78 to 200° C., preferably −10 to 150° C. Compound (XIV) can also be produced by subjecting an aldol intermediate obtained in the presence of a base such as lithium diisopropylamide to dehydration at room temperature or under heat in the presence of an acid catalyst such as p-toluenesulfonic acid. The product (XIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (X) can be produced by subjecting compound (V) or compound (XIV) to cyclization. The cyclization is conducted by a per se known method, for example, a method by heating, a method using an acidic substance, a method comprising the reaction with a halogenating agent and then conducting cyclization in the presence of a Lewis acid, or methods analogous thereto.

The cyclization under heating is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 10 hours. The reaction temperature is generally 100 to 300° C., preferably 100 to 200° C.

In the case where the cyclization is conducted by using an acid substance, the acidic substance includes, for example, phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrochloric acid, sulfuric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (V) or compound (XIV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

In the case where the cyclization is conducted in the presence of a Lewis acid after compound (V) is allowed to react with a halogenating agent, the halogenating agent is examplified thionyl halides such as thionyl chloride, thionyl bromide, etc.; phosphoryl halides such as phosphoryl chloride, phosphoryl bromide, etc.; phosphorus halides such as phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide, phosphorus tribromide, etc.; oxalyl halides such as oxalyl chloride, etc.; phosgene, etc. The halogenating agent is used in an amount of approximately 1.0 to 30 mols, preferably approximately 1.0 to 10 mols per mol of compound (V). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 10 minutes to 5 hours. The reaction temperature is generally −10 to 200° C., preferably −10 to 120° C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. The Lewis acid to be used in the next cyclization includes, for example, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid is used in an amount of approximately 0.1 to 20 mols, preferably approximately 0.2 to 5.0 mols per mol of compound (V). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; halogenated hydrocarbons such as monochlorobenzene, o-dichlorobenzene, 1,2,4-trichlorobenzene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally −20 to 200° C., preferably −5 to 120° C. The product (X) produced by the above-mentioned cyclization can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XII) can be produced by reacting a carbanion, which is formed by the treatment of acetonitrile

with a base, with compound (X) to give compound (XI) followed by dehydrating the resultant compound (XI). Compound (XII) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Acetonitrile is used in an amount of approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.3 mols per mol of compound (X). The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. These bases are used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (X). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally −78 to 100° C., preferably −78 to 50° C. The product obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

The catalyst to be used for the dehydration includes, for example, acidic catalysts such as hydrochloric acid, sulfuric acid, phosphoric acid, potassium hydrogensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, boron trifluoride-ether complex, etc.; basic catalysts such as sodium hydroxide, potassium hydroxide, etc. If desired, a dehydrating agent such as N,N'-dicyclohexylcarbodiimide, alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride or methanesulfonyl chloride can also be used. The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

Compound (XII) can also be produced by reacting a phosphonate-carbanion, which is produced by the treatment of a dialkyl cyanomethylphosphonate with a base, with compound (X). This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The dialkyl cyanomethylphosphonate includes, for example, diethyl cyanomethylphosphonate, etc. The dialkyl cyanomethylphosphonate is used in an amount of approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (X). The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (X). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 1 hour to 50 hours, preferably 1 hour to 10 hours. The reaction temperature is generally −78 to 200° C., preferably 0 to 150° C. The mixture of isomers of compound (XII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

The extension of the carbon chain at the side chain of compound (XII) can be conducted by means of per se known carbon chain extension reaction, for example, a reaction comprising hydrolysis of cyano group under alkaline or acidic conditions to convert into carboxyl group, or leading the carboxyl to ester form, which is then subjecting to reduction to give an alcohol, followed by halogenation and cyanation.

Compound (XV) can be produced by reducing compound (XII). The reducing agent to be used, includes, for example, metal hydrides such as aluminium hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, etc., or the hydrogenation catalyst to be used includes, for example, Raney nickel, Raney cobalt, etc. Regarding the amount of the reducing agent, the metal hydride is used in an amount of approximately 1.0 to 10 mols, preferably approximately 1.0 to 3.0 mols per mol of compound (XII) while the metal hydride complex is used in an amount of approximately 1.0 to 10 mols, preferably 1.0 to 3.0 mols per mol of compound (XII). For the hydrogenation, a catalyst such as Raney nickel or Raney cobalt is used in an amount of approximately 10 to 1000% by weight, preferably approximately 80 to 300% by weight relative to compound (XII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc., or a suitable mixture of these solvents are preferable. In the case where a catalyst such as Raney nickel or Raney cobalt is used, amines such as ammonia may be added to the reaction system in order to prevent any possible side reactions. The reaction time varies, depending on the activity of the catalyst and the amount thereof used, and is generally 1 hour to 100 hours, preferably 1 hour to 50 hours. The reaction temperature is generally 0 to 120° C., preferably 20 to 80° C. In the case where a catalyst such as Raney nickel or Raney cobalt is used, the hydrogen pressure is generally 1 to 100 atmo-

spheres. The product (XV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XVI) with m=2 or 3 can be produced by isomerizing compound (XV) with an acid. The acid catalyst to be used include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid catalyst is used in an amount of approximately 0.01 to 10 mols, preferably approximately 0.01 to 5.0 mols per mol of compound (XV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 10 minutes to 2 hours. The reaction temperature is generally −10 to 200° C., preferably −10 to 100° C. The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XVI) with m=1 can be produced by treating compound (X) with trimethylsilylcyanide in the presence of a Lewis acid, then treating the resultant intermediate with an acid to remove its trimethylsilyloxy group and thereafter reducing it at its cyano group. The Lewis acid includes, for example, zinc iodide, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid catalyst is used in an amount of approximately 0.01 to 10 mols, preferably approximately 0.01 to 1.0 mol per mol of compound (X). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 30 minutes to 3 hours. The reaction temperature is generally −10 to 200° C., preferably −10 to 100° C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. Next, the above product is treated with an acid. Preferably, the acid includes, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid is used in an amount of approximately 1 to 100 mols, preferably approximately 1 to 10 mols per mol of compound (X). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally 0 to 200° C., preferably 20 to 150° C. The reduction of the cyano group in the resultant compound can be conducted under the same conditions as those for the production of compound (XV) from compound (XII). The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XVII) can be produced by reacting compound (XVI) with a carboxylic acid or a salt thereof or a reactive derivative thereof. The carboxylic acid includes, for example, compounds of the formula R^1—COOH (in which R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole, benzotriazole, etc.), acid anhydrides (e.g., C_{1-6} aliphatic carboxylic acid anhydrides such as acetic acid anhydrides, propionic acid anhydrides, butyric acid anhydrides, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters (e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

In place of using the above reactive derivative, the carboxylic acid or its salt may be directly reacted with compound (XVI) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of R^1—COOH (in which R^1 is as defined above) or a reactive derivative thereof is used generally in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVI). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as

diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; water or a suitable mixture of these solvents are preferable. In the case where acid halides are used as the reactive derivatives of carboxylic acids, the reaction may be conducted in the presence of a de-acidifying agent in order to remove the released hydrogen halide from the reaction system. The de-acidifying agent includes, for example, basic salts such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally 30 minutes to 24 hours, preferably 30 minutes to 4 hours. The reaction temperature is generally 0 to 100° C., preferably 0 to 70° C.

Compound (XVII) can also be produced, while, accompanied by isomerization in the reaction system, by the following procedure, a carboxylic acid of the formula R^1—COOH (in which R^1 is as defined above) or its reactive derivative is added to compound (XV), and the mixture is stirred, under acidic conditions for 5 minutes to 3 hours, preferably 10 minutes to 1 hour, at 0 to 100° C., preferably 0 to 70° C., then the reaction mixture is subjected to acylation by adding the above-mentioned de-acidifying agent. The carboxylic acid or its reactive derivative is used generally in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XV). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The product (XVII) thus obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

For the production of optically active compound (XVII), a method, which comprises subjecting compound (XV) to reduction by using a catalyst for asymmetric reduction, e.g. a transition metal—optically active phosphine complex and, then, by subjecting the resultant to acylation, is employed. As the said transition metal—optically active phosphine complex, mention is made of, for example, ruthenium—optically active phosphine complex. Preferably, ruthenium-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl derivatives including diruthenium tetrachloro bis[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] triethylamine and [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate are employed. The reaction conditions are substantially the same as those for the production of an optically active aminoalkyl derivative from compound (XXXV) to be described later. The conditions of acylation of the optically active aminoalkyl derivative thus obtained are substantially the same as those for the production of compound (I) from compound (XXXVI) to be described later.

And, for the production of the optically active compound (XVII), a method, which comprises subjecting acylated compound (XV) to reduction by using a catalyst for asymmetric reduction, e.g. a transition metal—optically active phosphine complex, is employed as well. As the transition metal—optically active phosphine complex, mention is made of, for example, ruthenium—optically active phosphine complex. Preferably, ruthenium-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl derivatives including diruthenium tetrachloro bis[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]triethylamine and [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate are employed. The reaction conditions are substantially the same as those for the production of an optically active aminoalkyl derivative from compound (XXXV) to be described later. Conditions for acylation of compound (XV) are substantially the same as those for the production of compound (I) from compound (XXXVI) to be described later.

To obtain compound (XVII) in which R^2 is an alkyl group, the acylated compound obtained in the above process is alkylated with a corresponding alkylating agent (e.g., alkyl halides and sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVII) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally −20 to 200° C., preferably −10 to 150° C. The product (XVII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods,

and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

To obtain compound (XVII) in which the double-bond moiety has been reduced, the double-bond moiety in compound (XVII) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

Compound (XVIII) can be produced by removing the protective group for the hydroxyl group in compound (XVII). The de-protecting step is conducted by the per se known means. For example, referred to is the disclosure in the chapter "Protection for Phenols and Catechols" in "Protective Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

Compound (XIX) can be produced by reacting compound (XVIII) with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XX) [wherein R^8 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxyl group, a nitro group, a cyano group or an optionally substituted amino group, R^9 represents a hydrocarbon group and the other symbols are as defined above] can be produced by reacting compound (XVIII) with a corresponding α-haloketone (e.g., α-chloroketone, α-bromoketone, α-iodoketone, etc.) in the presence of a base. The α-haloketone is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXI) can be produced by reacting compound (XVIII) with a corresponding alkylating agent (e.g., substituted acetylenealkyl halides, sulfonates with substituted acetyleue alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 20 mols, preferably approximately 1.0 to 10 mols per mol of compound (XVIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as

N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XXI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (I) can be produced by per se known cyclization of compound (XIX), (XX) or (XXI). The cyclization can be conducted by, for example, a method by heating the compound, a method using an acidic substance, a method using a basic substance, or methods analogous thereto.

The cyclization under heating is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, bromobenzene etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc.; N,N-dimethylaniline, N,N-diethylaniline, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 10 hours. The reaction temperature is generally 100 to 300° C., preferably 150 to 250° C.

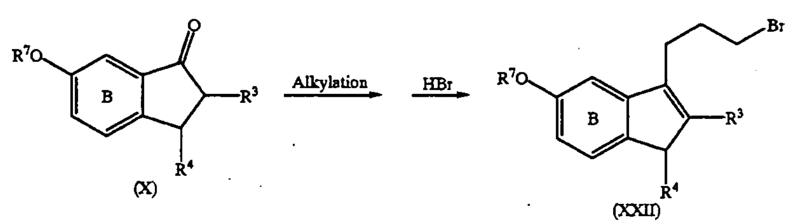
In the case where the cyclization is conducted by using an acid substance, the acidic substance includes, for example, phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrobromic acid, hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (XIX), (XX) or (XXI). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

In the case where the cyclization is conducted by using an basic substance, the basic substance includes, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc. The basic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (XIX), (XX) or (XXI). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

The product (I) obtained by the above-mentioned cyclization can be isolated from the reaction mixture by per se known methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

To obtain compound (I) in which the double-bond moiety has been reduced, the double-bond moiety in compound (I) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

Reaction Process 2:



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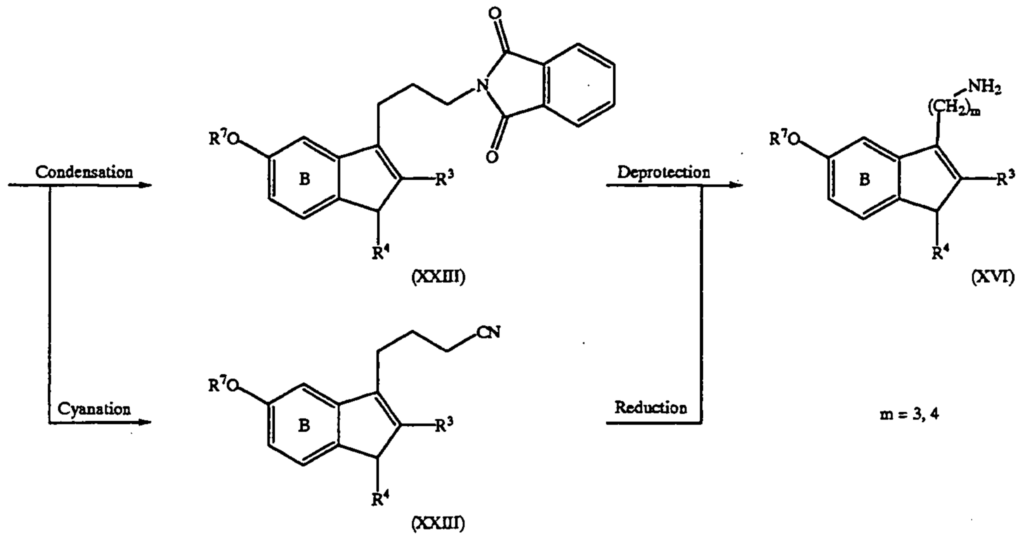


Compound (XXII) can be produced by alkylating compound (X) followed by treating it with hydrobromic acid. For the alkylation, a Grignard reagent to be prepared from cyclopropyl bromide and magnesium is diluted with an inert solvent and then applied to compound (X). The production of the Grignard reagent from cyclopropyl bromide may be conducted by known methods. Magnesium is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols, per mol of cyclopropyl bromide. The reaction is advantageously conducted in a solvent inert to the reaction.

so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 10 hours, preferably 15 minutes to 3 hours. The reaction temperature is generally 0 to 150° C., preferably 40 to 80° C. A small amount of iodine may be present in the reaction system. The Grignard reagent thus produced is left at room temperature to complete the reaction. Then, after removing the solvent through distillation or without removing it, the Grignard reagent is diluted with a solvent added thereto, and compound (X) is dropwise added to and reacted with the reagent. Compound (X) is used in an amount of approximately 0.4 to 3.0 mols, preferably approximately 0.4 to 1.0 mol per mol of the Grignard reagent. The solvent to be used for diluting the Grignard reagent is not specifically defined so far as the intended reaction advances therein, and includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; halogenated hydrocarbons such as chlorotoluene, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., or a suitable mixture of these solvents are preferable. The amount of the solvent to be used for the dilution may be approximately 1.0 to 30 times by volume, preferably approximately 1.0 to 15 times by volume, relative to the Grignard reagent. The reaction time is generally 10 minutes to 10 hours, preferably 15 minutes to 3 hours. The reaction temperature is generally 0 to 150° C., preferably 40 to 100° C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. The amount of the hydrobromic acid to be used is approximately 1.0 to 30 mols, preferably approximately 1.0 to 5.0 mols per mol of compound (X). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; organic acids such as formic acid, acetic acid, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 1 to 60 hours, preferably 1 to 15 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 80° C. The product (XXII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

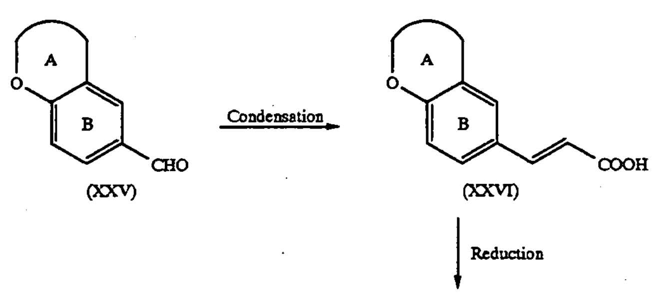
Compound (XXIII) can be produced by reacting compound (XXII) with a potassium phthalimide. The potassium phthalimide is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (XXII). The condensation of compound (XXII) with potassium phthalimide is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction and optionally in the presence of a base. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium

hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The amount of the base to be used is approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXII). Preferably, the solvent includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents. The reaction time is generally 30 minutes to 20 hours, preferably 30 minutes to 8 hours. The reaction temperature is generally 0 to 150° C., preferably 20 to 80° C. The product (XXIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXIV) can be produced by reacting compound (XXII) with a cyano compound. The cyano compound includes, for example, sodium cyanide, potassium cyanide and a mixture thereof. It may be produced in the reaction system by reacting hydrogen cyanide with a basic material such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate. The cyano compound is used in an amount of approximately 0.8 to 10 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, ortho-dichlorobenzene, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. A combination of water and a water-insoluble or hardly water-soluble organic solvent such as that selected from the above solvents can also be employed in the presence of a phase-transfer catalyst. The phase-transfer catalyst includes, for example, quaternary ammonium salts such as tetrabutylammonium bromide, benzyltriethylammonium chloride, etc.; and quaternary phosphonium salts. The phase-transfer catalyst is used in amount of approximately 0.001 to 10 mols, preferably approximately 0.005 to 0.5 mols per mol of compound (XXII). The reaction time is generally 30 minutes to 20 hours, preferably 30 minutes to 8 hours. The reaction temperature is generally 0 to 200° C., preferably 20 to 150° C. The product (XXIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XVI) can be produced by decomposing the imido group in compound (XXIII). For this, in general, 1 mol of compound (XXIII) is treated with approximately from 1.0 to 20 mols, preferably approximately from 1.0 to 5.0 mols of amines such as methylamine, ethylamine, etc., hydrazines such as hydrazine, phenylhydrazine, etc., alkali metal sulfides such as sodium sulfide, potassium sulfide, etc., mineral acids such as hydrochloric acid, sulfuric acid, etc. The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally 0 to 200° C., preferably 20 to 100° C. The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. Compound (XVI) can also be produced by reducing the cyano group in compound (XXIV) in the same manner as in the production of compound (XV) from compound (XII).

Reaction Process 3:



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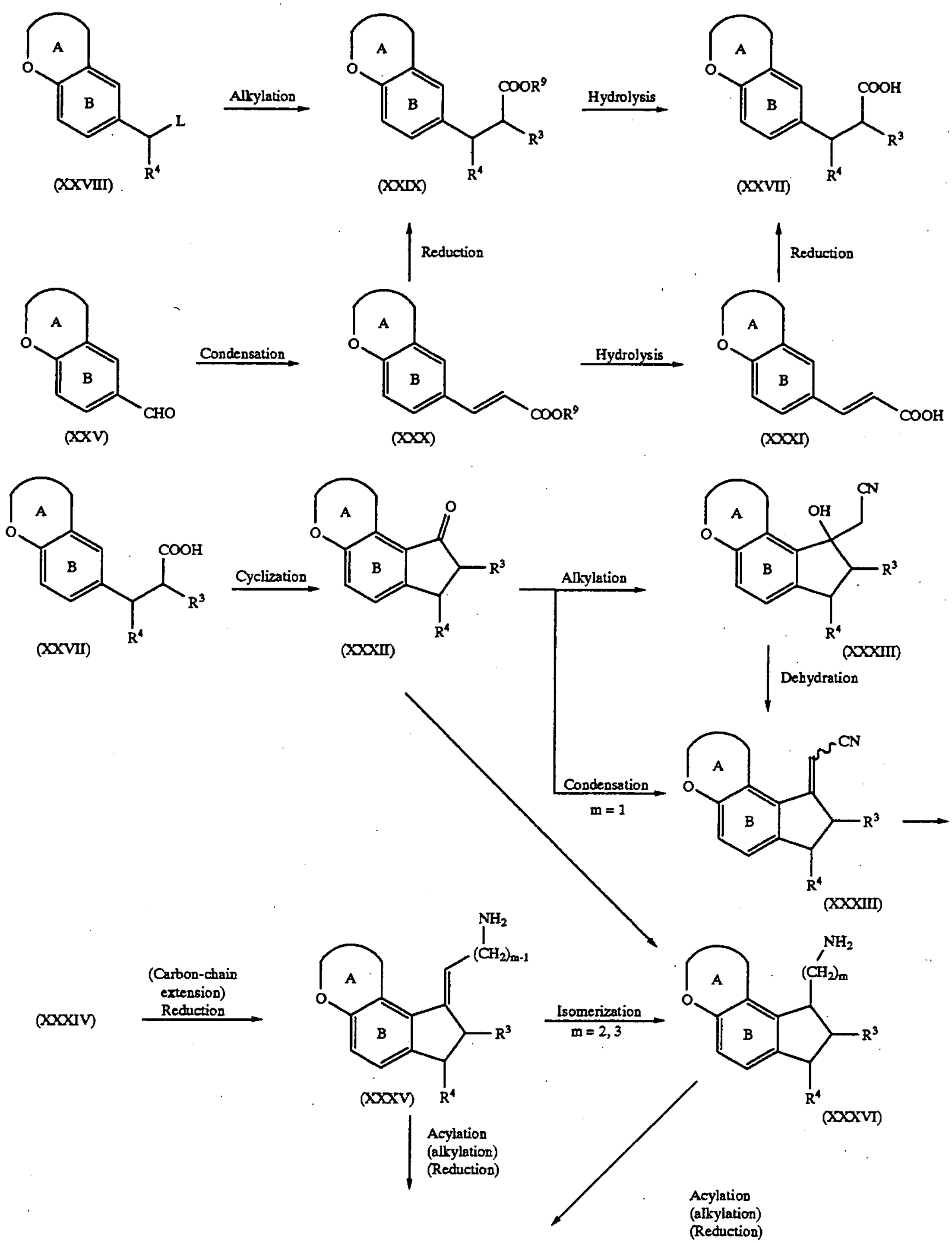
A
B
O
L
R4
(XXVIII)
Alkylation
COOR9
R3
(XXIX)
Hydrolysis
COOH
(XXVII)
Reduction
Reduction
CHO
(XXV)
Condensation
(XXX)
(XXXI)
Cyclization
(XXXII)
Alkylation
OH
CN
(XXXIII)
Dehydration
Condensation
m = 1
(XXXIV)
(Carbon-chain extension) Reduction
NH2
(CH2)m-1
(XXXV)
Isomerization
m = 2, 3
(CH2)m
(XXXVI)
Acylation
(alkylation)
(Reduction)

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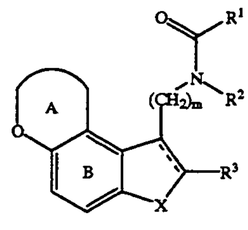


(I)(X = CHR^4)

Compound (XXV) can be produced by per se known methods, for example, the methods described in J. Org. Chem., Vol. 49, p. 409 (1984) and J. Indian Chem. Soc., Vol. 36, p. 76 (1959), or methods analogous thereto.

Compound (XXVIII) (wherein L represents a leaving group such as a halogen atom, an alkylsulfonyl group, an alkylsulfonyloxy group or an arylsulfonyloxy group.) can be produced by per se known methods, for example, the methods described in J. Chem. Soc., p. 2455 (1956) and ibid., p. 4665 (1958), or methods analogous thereto.

The halogen atom to be represented by L includes, for example, fluorine, chlorine, bromine, iodine, etc. The alkylsulfonyl group to be represented by L includes, for example, a C_{1-5} alkylsulfonyl group (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc. The alkylsulfonyloxy group to be represented by L includes, for example, an optionally halogenated C_{1-5} alkylsulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.), etc. The arylsulfonyloxy group to be represented by L includes, for example, an optionally substituted benzenesulfonyloxy group (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy, etc.), etc.

As the compounds in the above-mentioned reaction schemes are commercial products, if available, they can be directly used.

Compound (XXVI) can be produced from compound (XXV) and malonic acid through the Knoevenagel condensation thereof in the presence of a base, in the same manner as in the production of compound (IV) from compound (III) mentioned hereinabove. One mol of compound (XXV) is reacted with approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols of malonic acid. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, pyridine, 4-dimethylaminopyridine, N,N-dimethylaniline, piperidine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of approximately 0.1 to 10.0 mols, preferably approximately 0.1 to 5.0 mol per mol of compound (XXV). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time varies, depending on the reagents and solvents used, and is generally 30 minutes to 24 hours, preferably 30 minutes to 8 hours. The reaction temperature is generally 0 to 150° C., preferably 0 to 130° C. The product (XXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXX) can be produced by reacting a phosphonate-carbanion, which is produced by the treatment of a trialkyl phosphonoacetate with a base, with compound (XXV), in the same manner as in the production of compound (VIII) from compound (III) mentioned hereinabove. This compound (XXX) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. As mentioned hereinabove, the trialkyl phosphonoacetate includes, for example, ethyl diethylphosphonoacetate, etc. One mol of compound (XXV) is reacted with approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.5 mols of a dialkyl alkylphosphonate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols, per mol of compound (XXV). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 1 hour to 50 hours, preferably 1 hour to 10 hours. The reaction temperature is generally −78 to 200° C., preferably 0 to 150° C. The mixture of isomers of compound (XXX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXXI) can be produced by hydrolyzing the ester moiety of compound (XXX) with an acid or base, in the same manner as in the production of compound (IX) from compound (VIII) mentioned hereinabove. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoro-

acetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately 0.5 to 10 mols, preferably approximately 0.5 to 3.0 mols per mol of compound (XXX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 60 hours, preferably 10 minutes to 12 hours. The reaction temperature is generally −10 to 200° C., preferably from 0 to 120° C. The product (XXXI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXIX) can be produced by reacting compound (XXVIII) and an ester derivative of the formula $R^3CH_2COOR^9$ (in which R^3 and R^9 are as defined above) in the presence of a base, in the same manner as in the production of compound (VII) from compound (VI) mentioned hereinabove. The "hydrocarbon group" to be represented by R^9 includes, for example, the above-mentioned "hydrocarbon group". Of the examples of the hydrocarbon group as mentioned above, R^9 is preferably a lower alkyl group (e.g., a C_{1-6} alkyl group such as methyl, ethyl, isopropyl, etc.) or an optionally substituted benzyl group. The "optionally substituted benzyl group" may have one to three substituents such as halogen atoms or C_{1-3} alkyl groups, at any substitutable position in the benzyl group. Concretely, it includes, for example, benzyl, p-chlorobenzyl, p-methylbenzyl, etc.

The ester derivative is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXVIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXVIII). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally −20 to 200° C., preferably −10 to 150° C. The product (XXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXIX) can also be produced by catalytically reducing compound (XXX) in a hydrogen atmosphere in the presence of various catalysts, in the same manner as in the catalytic reduction of compound (VIII) into compound (VII) mentioned hereinabove. The catalysts to be used for the reduction include, for example, platinum oxide, platinum on activated carbon, palladium on activated carbon, palladium on barium sulfate, nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. The amount of the catalyst to be used may be approximately 5 to 1000% by weight, preferably approximately 5 to 300% by weight relative to compound (XXX). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; water, etc., or a suitable mixture of these solvents are preferable. The reaction time varies, depending on the activity of the catalyst and the amount thereof used. In general, it is 30 minutes to 24 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 120° C., preferably 20 to 80° C. The pressure for the reaction is generally 1 to 100 atmospheres. Additives (promoters) that enhance the activity of the catalyst used can be added to the reaction system. Acidic additives advantageously usable for this purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. The product (XXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXVII) can be produced by catalytically reducing compound (XXVI) or compound (XXXI) in a hydrogen atmosphere in the same manner as in the catalytic reduction of compound (XXX) into compound (XXIX) or in the catalytic reduction of compound (IV) or compound (IX) into compound (V) mentioned hereinabove.

Compound (XXVII) can also be produced by hydrolyzing the ester moiety of compound (XXIX) with an acid or base, in the same manner as in the production of compound (V) from compound (VII) mentioned hereinabove. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately 0.5 to 10 mols, preferably approximately 0.5 to 6.0 mols per mol of compound (XXIX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 60 hours, preferably 10 minutes to 12 hours. The reaction temperature is generally −10 to 200° C., preferably 0 to 120° C. The product (XXVII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXXII) can be produced by per se known cyclization of compound (XXVII), in the same manner as in the cyclization of compound (V) into compound (X) mentioned hereinabove. The cyclization can be conducted by, for example, a method by heating the compound, a method of using an acidic substance, a method comprising the reaction with a halogenating agent and then conducting cyclization in the presence of a Lewis acid, or methods analogous thereto.

The cyclization under heating is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 10 hours. The reaction temperature is generally 100 to 300° C., preferably 100 to 200° C.

In the case where the cyclization is conducted by using an acid substance, the acidic substance is exemplified phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrochloric acid, sulfuric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

In the case where the cyclization is conducted in the presence of a Lewis acid after compound (XXVII) is allowed to react with a halogenating agent, the halogenating agent to be used is exemplified thionyl halides such as thionyl chloride, thionyl bromide, etc.; phosphoryl halides such as phosphoryl chloride, phosphoryl bromide, etc.; phosphorus halides such as phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide, phosphorus tribromide, etc.; oxalyl halides such as oxalyl chloride, etc.; phosgene, etc. The halogenating agent is used in an amount of approximately 1.0 to 30 mols, preferably approximately 1.0 to 10 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 10 minutes to 5 hours. The reaction temperature is generally −10 to 200° C., preferably from −10 to 120° C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. The Lewis acid to be used in the next cyclization includes, for example, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid is used in an amount of approximately 0.1 to 20 mols, preferably approximately 0.2 to 5.0 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; halogenated hydrocarbons such as monochlorobenzene, o-dichlorobenzene, 1,2,4-trichlorobenzene,

dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally −20 to 200° C., preferably −5 to 120° C. The product (XXXII) obtained by the above cyclization can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

For causing these cyclization reactions to proceed predominantly in the desired direction, the cyclization may be carried out after substitution, with a halogen atom or atoms, of a position or positions on the benzene ring which are undesirable for the desired cyclization. In this case, the halogenation includes, for example, ordinary halogenation using a halogenating agent (e.g. halogen such as bromine or chlorine), halogeneation using a halogenating agent together with a metal catalyst such as iron, chlorination using titanium tetrachloride-trifluoroacetic acid, halogenation using a copper halide, chlorination using sulfuryl chloride-aluminum chloride, and so forth. Among these, the ordinary halogenation is preferred for the first-step halogenation and, when a next step halogenation is necessary, the method using iron as a catalyst is preferred. In this reaction, the halogenating agent is used in an amount of 0.8 to 3 moles, preferably 1 to 2 moles, per mole of compound (XXVII). The iron catalyst is used in an amount of 0.01 to 0.5 equivalent, preferably 0.05 to 0.2 equivalent, per mole of compound (XXVII). The reaction is carried out in the absence or presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethyl ether, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., organic acids such as acetic acid, propionic acid, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 10 hours, preferably 20 minutes to 5 hours. The reaction temperature is generally −20 to 120° C., preferably −10 to 80° C. It is also possible to effect two or three stages of halogenation in one step; in this case, the halogenating agent is used in an amount twice the amount mentioned above.

Compound (XXXIV) can be produced by reacting a carbanion, which is formed by the treatment of acetonitrile with a base, with compound (XXXII) to obtain compound (XXXIII) followed by dehydrating the resultant compound (XXXIII), in the same manner as in the production of compound (XII) from compound (X) mentioned hereinabove. Compound (XXXIV) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Acetonitrile is used in an amount of approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.3 mols per mol of compound (XXXII). The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (XXXII). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally −78 to 100° C., preferably −78 to 50° C. The product obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

The catalyst to be used for the dehydration includes, for example, acidic catalysts such as hydrochloric acid, sulfuric acid, phosphoric acid, potassium hydrogensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, boron trifluoride-ether complex, etc., and basic catalysts such as sodium hydroxide, potassium hydroxide, etc. If desired, a dehydrating agent such as N,N-cyclohexylcarbodiimide as well as alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, etc. can also be used. The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

Compound (XXXIV) can also be produced by reacting a phosphonate-carbanion, which is produced by the treatment of a trialkyl phosphonoacetate with a base, with compound (XXXII), in the same manner as in the production of compound (XII) from compound (X) mentioned hereinabove. This compound (XXXIV) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The trialkyl phosphonoacetate includes, for example, diethyl cyanomethylphosphonate, etc. One mol of compound (XXXII) is reacted with approximately 1.0 to 3.0 mols, preferably approximately 1.0 to 1.5 mols of a trialkyl phosphonoacetate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 1.5 mols per mol of compound (XXXII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene,

toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 1 hour to 50 hours, preferably 1 hour to 10 hours. The reaction temperature is generally −78 to 200° C., preferably 0 to 150° C. The mixture of isomers of compound (XXXIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

In the case where the carbon chain at the side chain of compound (XXXIV) is extended, it can be conducted by per se known carbon-chain extension, for example, a reaction comprising hydrolysis of cyano group under alkaline or acidic conditions to convert into carboxyl group, or leading the carboxyl to ester form which is then subjecting to reduction to give an alcohol, followed by halogenation and cyanation.

Compound (XXXV) can be produced by reducing compound (XXXIV), in the same manner as in the production of compound (XV) from compound (XII) mentioned hereinabove. The reducing agent usable for this includes, for example, metal hydrides such as aluminium hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, etc. The hydrogenation catalyst usable includes, for example, a catalyst such as Raney nickel, Raney cobalt, etc. Regarding the amount of the reducing agent, the metal hydride is used in an amount of approximately 1.0 to 10 mols, preferably approximately 1.0 to 3.0 mols per mol of compound (XXXIV), the metal hydride complex is used in an amount of approximately 1.0 to 10 mols, preferably 1.0 to 3.0 mols per mol of compound (XXXIV). For the hydrogenation, a catalyst such as Raney nickel or Raney cobalt is used in an amount of approximately 10 to 1000% by weight, preferably approximately 80 to 300% by weight relative to compound (XXXIV). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, anyone can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc., or a suitable mixture of these solvents are preferable. In the case where a Raney nickel or Raney cobalt catalyst is used, amines such as ammonia may be added to the reaction system in order to prevent any possible side reactions. The reaction time varies, depending on the activity of the catalyst and the amount thereof used, and is generally 1 hour to 100 hours, preferably 1 hour to 50 hours. The reaction temperature is generally 0 to 120° C., preferably 20 to 80° C. In the case where Raney nickel or Raney cobalt catalyst is used, the hydrogen pressure is generally 1 to 100 atmospheres. The product (XXXV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

And, by employing stronger reaction conditions for producing compound (XXXV) (e.g. conducting the reaction at higher temperatures and for a longer time), reduction of the double bond portion and reduction of silano group can be performed simultaneously.

For producing an optically active compound (I), a method, which comprises subjecting compound (XXXV) to reduction using, for example, a catalyst for asymmetric reduction, followed by subjecting the resultant to acylation, is employed.

As the catalyst for asymmetric reduction, mention is made of, for example, transition metal—optically active phosphine complexes. Examples of the transition metal—optically active phosphine complexes include ruthenium—optically active phosphine complexes. Among them, for example, a ruthenium-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl derivative such as diruthenium tetrachloro bis[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] triethylamine, is generally employed.

In the optically active tertiary phosphine in ruthenium—optically phosphine complexes, there exist two kinds of optical isomers, i.e. (R)- and (S)-isomers. By optionally selecting either one of (R)- or (S)-isomers of the optically active phosphine in the ruthenium—optically active phosphine complexes, the desired optically active compound can be obtained selectively (in substantially pure state).

The reduction reaction can be conducted under elevated pressure in, for example, an autoclave, under the hydrogen pressure described below, by heating and stirring.

The amount of ruthenium—optically active phosphine catalyst is, relative to compound (XXXV), ½ to 1/1000 times as much mol., preferably 1/10 to 1/500 times as much mol.

This reaction can be conducted in an organic solvent. Examples of the organic solvent include aromatic hydrocarbons such as toluene, benzene, chlorobenzene, etc.; aliphatic esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, etc.; ethers such as isopropyl ether, diethyl ether, tetrahydrofuran, etc.; halogenated hydrocarbons such as dichloromethane, dichloroethane, etc.; alcohols such as methanol, ethanol, isopropanol, etc.; amides such as N,N-dimethylformamide, etc.; or a mixture solvent of them. Among them, alcohols are preferable, and methanol is more preferable.

In the reaction, the volume of organic solvent is, relative to 1 weight part of compound (XXXV), usually 1 to 1000 times as much volume, preferably 2 to 20 times as much volume. The reaction temperature is usually 0 to 150° C., preferably 5 to 100° C., more preferably 10 to 80° C. The hydrogen pressure in the reaction ranges usually 5 to 150 kg/cm^2, preferably 30 to 110 kg/cm^2. The reaction time is usually 0.5 to 100 hours, preferably 1 to 50 hours, more preferably from 5 to 25 hours.

In the reaction, a Lewis acid, proton acid or the like may optionally added to the reaction mixture.

The reaction may be conducted, after adding to the reaction mixture beforehand the desired optically active compound among the compounds to be reduced, in an amount usually ranging, relative to 1 weight part of the starting compound (XXXV), from 1/200 to ⅓ times as much weight, preferably from 1/100 to 1/10 times as much weight.

The conversion rate of compound (XXXV) to the desired optically active compound can be determined by the following method.

Namely, an appropriate volume of the reaction mixture taken by sampling after completion of the reaction is subjected to high performance liquid chromatography (HPLC) using a per se known suitable chiral column [e.g. Chiralpak (manufactured by Daicel Chemical Industries Ltd.), ULTRON ES-OVM (SHINWA CHEMICAL INDUSTRIES LTD.)] so that the respective amounts of the desired optically active compounds can be determined.

From the reaction mixture obtained by the the above-mentioned reaction, optically active amine derivatives can be obtained by per se known methods (e.g. solvent extraction, phasic transfer, crystallization, recrystallization and chromatography).

The optically active compound (I) can be produced by subjecting the thus obtained optically active amine derivative to acylation. The reaction conditions are substantially the same as those for the production of compound (I) from compound (XXXVI) to be described later.

Compound (XXXVI) with m=2 or 3 can be produced by isomerizing compound (XXXV) with an acid, in the same manner as in the production of compound (XVI) from compound (XV) mentioned hereinabove. Preferred examples of the acid catalyst to be used include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid catalyst is used in an amount of approximately 0.01 to 10 mols, preferably approximately 0.01 to 5.0 mols per mol of compound (XXXV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 10 minutes to 2 hours. The reaction temperature is generally −10 to 200° C., preferably −10 to 100° C. The product (XXXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXXVI) with m=1 can be produced by treating compound (XXXII) with trimethylsilylcyanide in the presence of a Lewis acid, then treating the resultant intermediate with an acid to remove its trimethylsilyloxy group and thereafter reducing it at its cyano group, in the same manner as in the production of compound (XVI) from compound (X) mentioned hereinabove. The Lewis acid includes, for example, zinc iodide, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid catalyst is used in an amount of approximately 0.01 to 10 mols, preferably approximately 0.01 to 1.0 mol per mol of compound (XXXII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 12 hours, preferably 30 minutes to 3 hours. The reaction temperature is generally −10 to 200° C., preferably −10 to 100° C. The obtained intermediate can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography. Next, the intermediate is treated with an acid. Preferably, the acid includes, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid is used in an amount of approximately 1 to 100 mols, preferably approximately 1 to 10 mols per mol of compound (XXXII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 5 hours. The reaction temperature is generally 0 to 200° C., preferably 20 to 150° C. The reduction of the cyano group in the resultant intermediate can be conducted under the same conditions as those for the production of compound (XV) from compound (XII). The product (XXXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (I) can also be produced by reacting compound (XXXVI) with a carboxylic acid or a salt or a reactive derivative thereof. The carboxylic acid includes, for example, compounds of the formula R^1—COOH (in which R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole, benzotriazole, etc.), acid anhydrides (e.g., C_{1-6} aliphatic carboxylic acid anhydrides such as acetic acid anhydrides, propionic acid anhydrides, butyric acid anhydrides, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters (e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

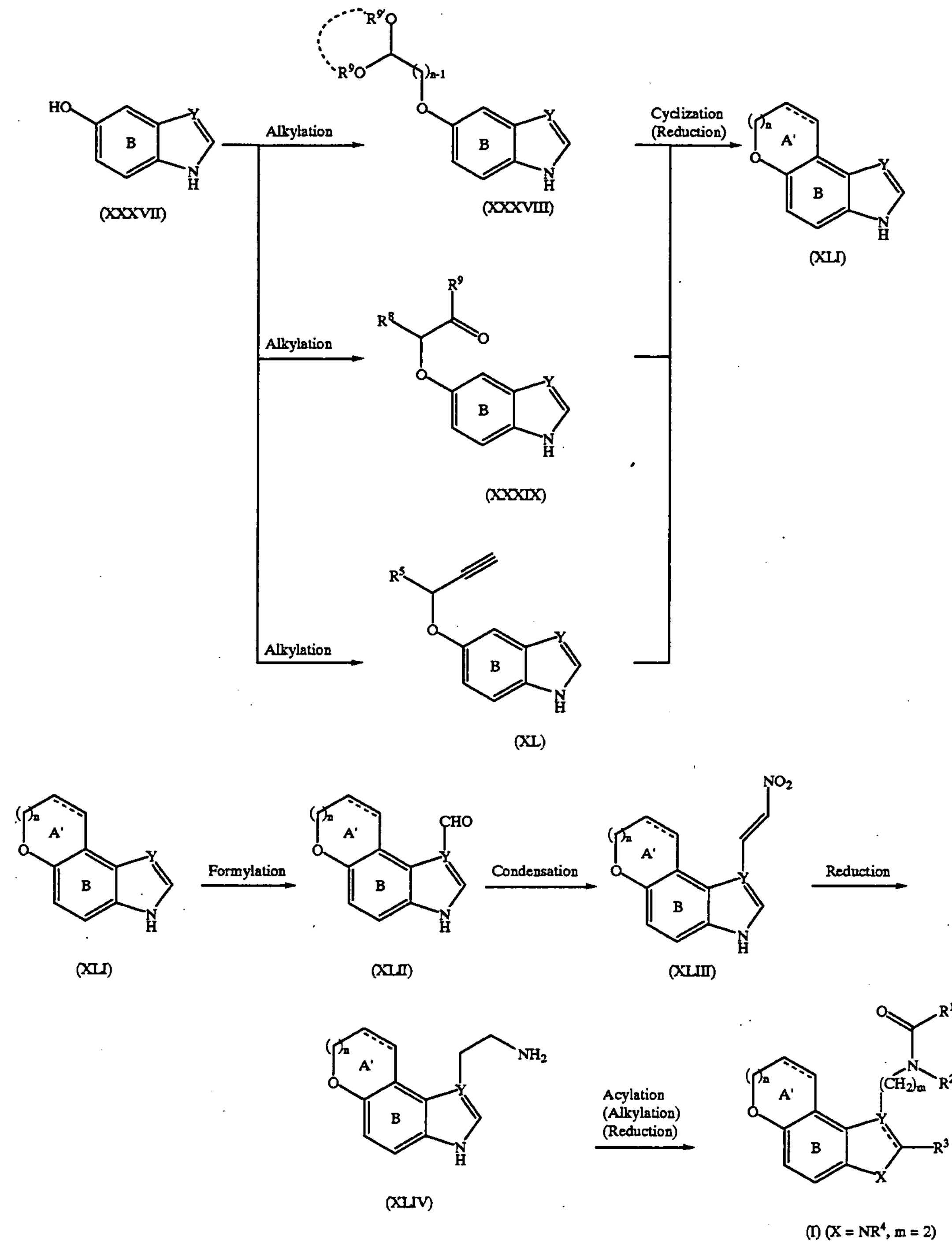
In place of using the reactive derivative, the carboxylic acid or a salt thereof may be directly reacted with compound (XXXVI) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of the formula R^1—COOH (in which R^1 is as defined above) or its reactive derivative is used generally at approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXXVI). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; water or a suitable mixture of these solvents are preferable. In the case where an acid halide is used as a reactive derivative of a carboxylic acid, the reaction may be conducted in the presence of a de-acidifying agent in order to remove the released hydrogen halide from the reaction system. The de-acidifying agent includes, for example, basic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally 30 minutes to 24 hours, preferably 30 minutes to 4 hours. The reaction temperature is generally 0 to 100° C., preferably 0 to 70° C.

Compound (I) can also be produced by treating compound (XXXV) with a carboxylic acid of the formula R^1—COOH (in which R^1 is as defined above), a salt or a reactive derivative thereof, stirring them under acidic conditions for 5 minutes to 3 hours, preferably 10 minutes to 1 hour, at 0 to 100° C., preferably 0 to 70° C., and thereafter adding a de-acidifying agent such as that mentioned above to the reaction system to thereby make the resultant intermediate acylated. The process can be accompanied by isomerization of the reaction system to give compound (I). The carboxylic acid or its reactive derivative is used generally in amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXXV). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The product (I) thus obtained can be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

To obtain compound (I) wherein R^2 is an alkyl group, the acylated compound as obtained in the above is alkylated with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (I) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (I). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally −20 to 200° C., preferably −10 to 150° C. The product (I) can be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

To obtain compound (I) wherein the double-bond moiety has been reduced, the double-bond moiety in compound (I) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

Reaction Process 4:



Compound (XXXVII) can be produced by per se known methods, for example, the methods described in J. Chem. Soc., p. 2525 (1952); ibid., p. 1165 (1954); J. Org. Chem. Vol. 49, p. 4833 (1984); J. Heterocyclic Chem., Vol. 24, p. 941 (1987); J. Med. Chem., Vol. 17, p. 747 (1974); Helv. Chim. Acta, Vol. 48, p. 252 (1965), or methods analogous thereto.

Compound (XXXVIII) can be produced by reacting compound (XXXVII) with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately 0.5 to 5.0 mols, preferably approximately 0.8 to 2.0 mols per mol of compound (XXXVII) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic

salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XXXVIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XXXIX) can be produced by reacting compound (XXXVII) with a corresponding α-haloketone in the presence of a base. The α-haloketone is used in an amount of approximately 1.0 to 10.0 mols, preferably approximately 1.0 to 5.0 mols per mol of compound (XXXVII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XXXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XL) can be produced by reacting compound (XXXVII) with a corresponding alkylating agent (e.g., substituted acetylene-alkyl halides, sulfonates with substituted acetylene alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 20.0 mols, preferably approximately 1.0 to 10.0 mols per mol of compound (XXXVII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours. The reaction temperature is generally −20 to 200° C., preferably 0 to 150° C. The product (XL) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

In the above-mentioned alkylation, if the alkylation is not selectively directed towards the hydroxyl group of the compound, the amino group of the compound shall be protected and de-protected, if necessary. The protection and the de-protection of the amino group may be conducted in accordance with conventional known methods. For example, referred to is the disclosure in the chapter "Protection for the Amino Group" in "Protecting Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

Compound (XLI) can be produced by per se known cyclization of compound (XXXVIII), (XXXIX) or (XL). The cyclization can be conducted by, for example, a method by heating, a method using an acidic substance, a method using a basic substance, or methods analogous thereto.

The cyclization under heating is advantageously conducted in either the absence of a solvent or the presence of

a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, bromobenzene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc.; N,N-dimethylaniline, N,N-diethylaniline, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 10 hours. The reaction temperature is generally 100 to 300° C., preferably 100 to 250° C.

In the case where the cyclization is conducted by using an acidic substance, the acidic substance includes, for example, phosphorus oxychloride, phosphorus pentachloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrochloric acid, hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (XXXVIII), (XXXIX) or (XL). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

In the case where the cyclization is conducted by using a basic substance, the basic substance includes, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc. The basic substance is used in an amount of approximately 0.5 to 100 mols, preferably approximately 5.0 to 20 mols per mol of compound (XXXVIII), (XXXIX) or (XL). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 12 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally 0 to 200° C., preferably 0 to 150° C.

The double-bond moiety in the ring as newly formed by the above cyclization may optionally be reduced in the same manner as in the production of compound (VII) from compound (VIII).

The product (XLI) obtained through the cyclization can be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XLII) can be produced from compound (XLI) in accordance with per se known methods, for example, the methods described in The Chemistry of Heterocyclic Compounds, Vol. 25, Part 3 (W. J. Houlihan, ed., John Wiley and Sons, Inc., New York), p. 361 (1979); J. Chem. Soc., p. 3842 (1954); Tetrahedron, Vol. 36, p. 2505 (1980); Monatsh. Chem., Vol. 117, p. 375 (1986), or methods analogous thereto.

Compound (XLIII) can be produced from compound (XLII) and nitromethane through aldol condensation in the presence of a base. This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Nitromethane is used in an amount of approximately 1.0 to 100 mols, preferably approximately 1.0 to 50 mols per mol of compound (XLII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; primary amines such as methylamine, propylamine, butylamine, benzylamine, aniline, etc.; ammonium acetate, alumina, etc. The base is used in an amount of approximately 0.01 to 5.0 mols, preferably 0.1 to 1.0 mol per mol of compound (XLII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; water, or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 72 hours, preferably 30 minutes to 24 hours. The reaction temperature is generally −20 to 200° C., preferably from −10 to 150° C. The product (XLIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XLIV) can be produced by reducing compound (XLIII). The reducing agent usable for this includes, for example, metal hydrides such as aluminium hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, lithium borohydride, sodium borohydride cyanide, etc. As the hydrogenation catalyst, for example, usable are Raney nickel, platinum oxide, platinum on activated carbon, palladium on activated carbon, palladium on barium sulfate, nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. Additives (promoters) that enhance the activity of a catalyst used can be added to the reaction system. Acidic additives advantageously usable for this purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. Regarding the amount of the reducing agent to be used, the metal hydride is used in an amount of approximately 1.0 to 10 mols, preferably approximately 1.0 to 3.0 mols per mol of compound (XLIII), and the metal hydride complex is used in an amount of approximately 1.0 to 10 mols, preferably 1.0 to 3.0 mols per mol of compound (XLIII). For the hydrogenation, a catalyst such as Raney nickel or Raney cobalt is used in an amount of approximately 10 to 1000% by weight, preferably approximately 100 to 300% by weight relative to compound (XLIII). The reaction is advantageously conducted in a solvent inert thereto. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene,

toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc., or a suitable mixture of these solvents are preferable. The reaction time varies, depending on the activity of the catalyst or the reducing agent and the amount thereof used, and is generally 1 hour to 100 hours, preferably 1 hour to 50 hours. The reaction temperature is generally 0 to 120° C., preferably 20 to 80° C. In the case where Raney nickel or the like catalyst is used, the hydrogen pressure shall be generally 1 to 100 atmospheres. The product (XLIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (XLIV) can also be produced in accordance with per se known methods, for example, the methods described in J. Med. Chem., Vol. 35, p. 3625 (1992); Tetrahedron, Vol. 48, p. 1039 (1992), or methods analogous thereto.

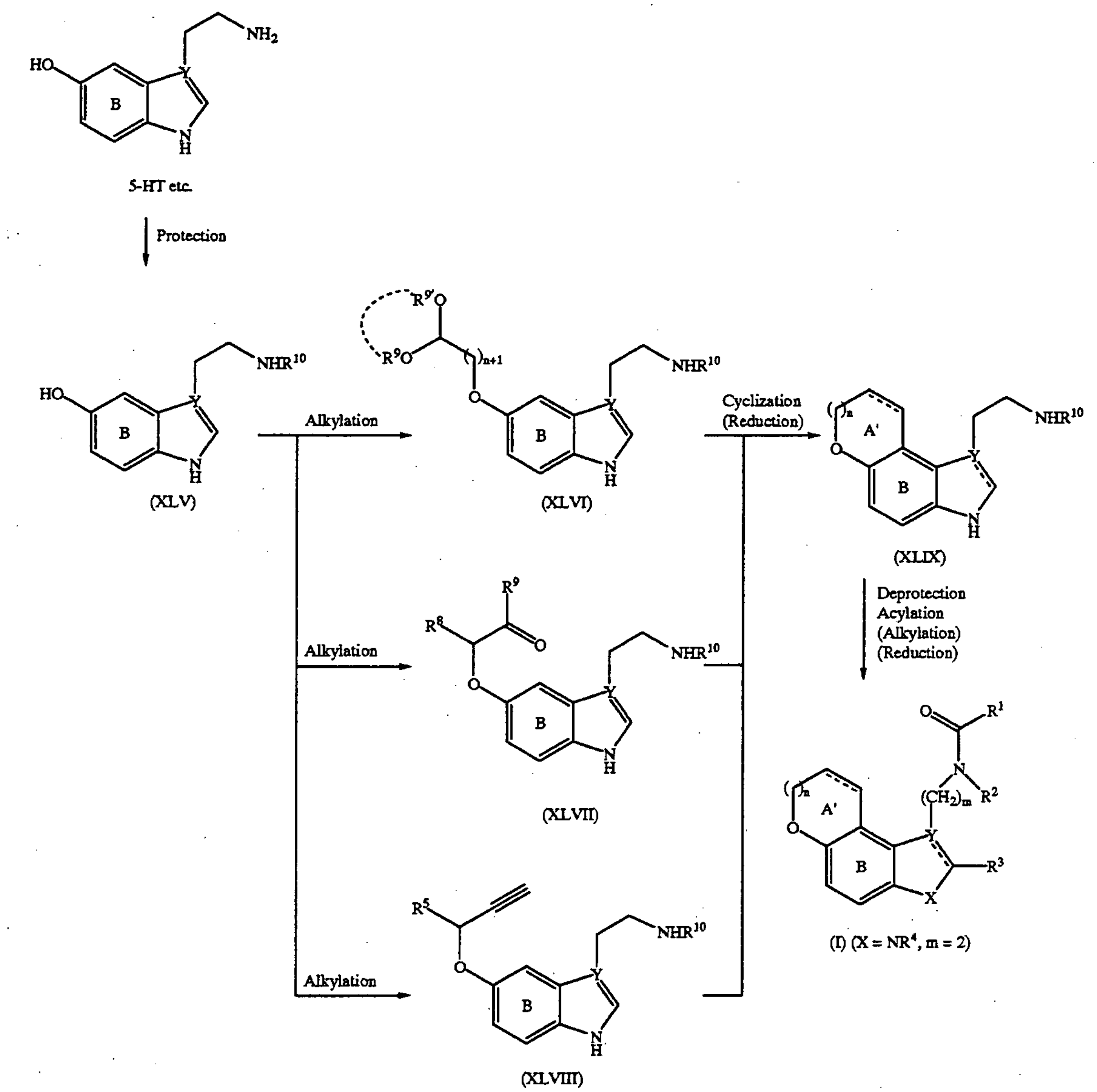
Compound (I) can be produced by reacting compound (XLIV) with a carboxylic acid or a salt thereof or a reactive derivative thereof. The carboxylic acid includes, for example, compounds of the formula R^1-COOH (in which R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole, benzotriazole, etc.), acid anhydrides (e.g., C_{1-6} aliphatic carboxylic acid anhydrides such as acetic acid anhydrides, propionic acid anhydrides, butyric acid anhydrides, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters (e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

In place of using the reactive derivative, the carboxylic acid or its salt may be directly reacted with compound (XLIV) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of the formula R^1-COOH (in which R^1 is as defined above) or its reactive derivative is used generally in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (XLIV). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; water or a suitable mixture of these solvents are preferable. In the case that acid halides are used as the reactive derivatives of carboxylic acids, the reaction may be conducted in the presence of a deacidifying agent in order to remove the released hydrogen halide from the reaction system. The deacidifying agent includes, for example, basic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally 30 minutes to 24 hours, preferably 30 minutes to 4 hours. The reaction temperature is generally 0 to 100° C., preferably 0 to 70° C.

To obtain compound (I) wherein R^2 is an alkyl group, the acylated compound as obtained in the above is alkylated with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (I) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately 1.0 to 5.0 mols, preferably approximately 1.0 to 2.0 mols per mol of compound (I). The reaction is advantageously conducted in a solvent inert to the reaction. While, as the solvent, any one can be used so far as the reaction advances therein, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc., or a suitable mixture of these solvents are preferable. The reaction time is generally 30 minutes to 48 hours, preferably 30 minutes to 6 hours. The reaction temperature is generally −20 to 200° C., preferably −10 to 150° C. The product (I) can be isolated from the reaction mixture by ordinary methods, and it can be easily purified by means of separation, for example, recrystallization, distillation and chromatography.

Compound (I) in which the double-bond moiety has been reduced can be produced in the same manner as in the production of compound (VII) from compound (VIII).

Reaction Process 5:



Compound (XLV) can be produced by, for example, protecting the primary amino group of 5-hydroxytryptamine (5-HT). R^{10} represents a protective group and the "protective group" includes those "amino-protecting group" mentioned later herein. The protection of the amino group may be conducted in accordance with per se known methods. For example, referred to is the disclosure in the chapter "Protection for the Amino group" in "Protecting Groups in Organic Synthesis" by T. W. green (2nd Ed., 1991).

Compound (XLVI) can be produced from compound (XLV) in the same manner as in the production of compound (XXXVIII) from compound (XXXVII).

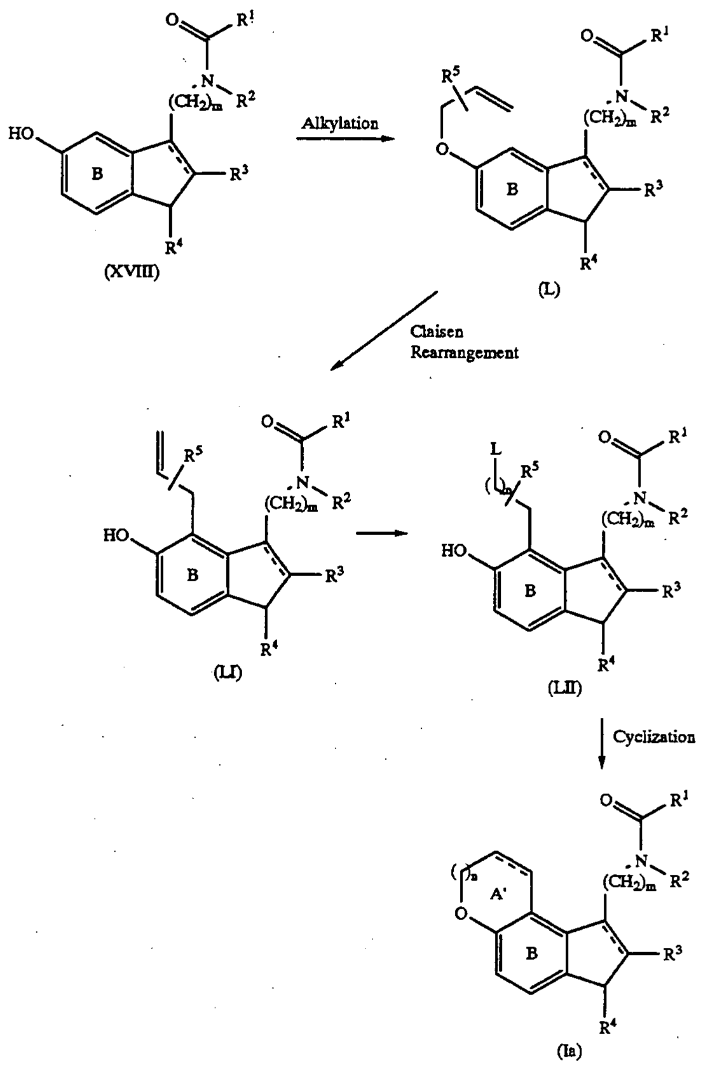
Compound (XLVII) can be produced from compound (XLV) in the same manner as in the production of compound (XXXIX) from compound (XXXVII).

Compound (XLVIII) can be produced from compound (XLV) in the same manner as in the production of compound (XL) from compound (XXXVII).

Compound (XLIX) can be produced from compound (XLVI), (XLVII) or (XLVIII) in the same manner as in the production of compound (XLI) from compound (XXXVIII), (XXXIX) or (XL). It can also be produced by per se known methods, for example, the methods described in Tetrahedron Lett., Vol. 36, p. 7019 (1995) or methods analogous thereto. Compound (XLIX) in which the double-bond moiety has been reduced can be produced in the same manner as in the production of compound (VII) from compound (VIII).

Compound (I) can be produced by de-protecting the protected amino group at the side chain in compound (XLIX) followed by processing the resultant compound in the same manner as in the production of compound (I) from compound (XLIV). The de-protection of the amino group may be conducted by per se known methods. For example, referred to is the disclosure in chapter "Protection for the Amino Group" in "Protecting Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

Reaction Process 6:



Compound (L) can be produced by allowing compound (XVIII) to react with a corresponding alkylating agent (e.g. substituted allyl halide or sulfonic acid ester of substituted allyl alcohol) in the presence of a base. Relative to 1 mol. of compound (XVIII), about 1.0 to 20.0 mol., preferably about 1.0 to 10.0 mol., of the alkylating agent is used. Examples of the base include basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methyl pyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyl disilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide and potassium tertiary butoxide, etc. Relative to 1 mol. of compound (XVIII), about 1.0 to 5.0 mol., preferably about 1.0 to 2.0 mol., of the base is used. It is advantageous to conduct this reaction using an inert solvent. As the solvent, any one can be used so long as it does not hamper the proceeding of the reaction. Preferable examples of the solvent include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.: hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethyl sulfoxide, etc.; and a mixture of these solvents. The reaction time is usually 30 minutes to 48 hours, preferably one hour to 24 hours. The reaction temperature is usually -20 to 200° C., preferably 0 to 150° C. While the product (L) can be used for the subsequent reaction as in the state of reaction mixture or as a crude product, it can optionally be isolated from the

reaction mixture by a conventional method and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (LI) can be produced by subjecting compound (L) to Claisen rearrangement reaction. The Claisen rearrangement reaction can be conducted by a per se known method described in, for example, "Shin Jikken Kagaku Koza Vol.14—Syntheses and Reactions of Organic Compounds (I), 3.2 Phenol, p.559 (compiled by The Chemical Society of Japan), Organic Reactions, Vol.2, pp.1–48, Vol.22, pp.1–252, or methods analogous to them. Concretely to state, the rearrangement reaction proceeds by heating compound (LI) in the absence or presence of a solvent. As the solvent, use is made of solvents having high boiling points, such as N,N-diethylaniline, diphenyl ether, 1,2,3,4-tetramethyl benzene, etc. The reaction time is usually 30 minutes to 48 hours, preferably one hour to 24 hours. The reaction temperature is usually 150 to 250° C., preferably 180 to 220° C. While the product (LI) can be used for the subsequent reaction as in the state of the reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method and can be easily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (LII) can be produced by oxidatively cleaving the double bond of compound (LI), followed by subjecting the compound to reduction. The leaving group represented by L in compound (LII) is preferably a hydroxy, halogen atoms, alkylsulfonate, arylsulfonate. The oxidative cleavage can be conducted by a per se known method using, for example, permanganate, permanganate-periodate, chromic acid, lead tetraacetate-N_3 complex, ozone, osmium tetroxide-hydrogen peroxide, osmium tetroxide-periodic acid, ruthenium tetroxide, iodosyl compound, oxygen, hydrogen peroxide or organic peroxide, organic peracid, nitrobenzene and anodic oxidation, a method described in, for example, Shin Jikken Kagaku Koza, Vol.15—Oxidation and Reduction—(compiled by The Chemical Society of Japan), or methods analogous to them. In the case of ozone oxidation, for example, while any solvent can be used so long as it does not hamper the proceeding of the reaction, for example, alcohols such as methanol, ethanol and propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-diethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; esters such as ethyl acetate, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, etc.; sulfoxides such as dimethyl sulfoxide; or a mixture of them. The reaction time, depending on the capacity of the ozone generator, is usually 5 minutes to 48 hours, preferably 5 minutes to 12 hours. The reaction temperature is usually −100 to 0° C., preferably −75 to −20° C. As the reducing agent to be employed in the subsequent reduction, use is made of, for example, metal hydrides such as aluminum hydride and diisobutyl aluminum hydride, and metal hydride complex compounds such as lithium aluminum hydride and sodium borohydride. The amount of the reducing agent to be used, in the case of a metal hydride for example, is about 1.0 to 20 mol., preferably about 1.0 to 10 mol., relative to 1 mol. of compound (LI), and, in the case of a metal hydride complex compound, it is about 1.0 to 20 mol., preferably about 1.0 to 10 mol., relative to 1 mol. of compound (LI). Use of a solvent inert to the reaction is advantageous for conducting this reaction. As such solvent, while any one can be used so long as the reaction proceeds, alcohols such as methanol, ethanol, propanol, etc,; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; or a mixture solvent of them are preferable. While the reaction time varies with the activity and amount of the reagent then employed, it usually is 5 minutes to 100 hours, preferably 5 minutes to 50 hours. The reaction temperature is usually −78° C. to 120° C., preferably from −78° C. to 50° C. While compound (LII) can be used for the subsequent reaction as it is or as a crude product, it can be isolated from the reaction mixture by a conventional method, which can readily be purified by means of recrystallization, distillation and chromatography.

Compound (Ia) can be produced by subjecting compound (LII) (wherein L is hydroxy), after converting to a sulfonate compound or a halogenate, to ring closure reaction.

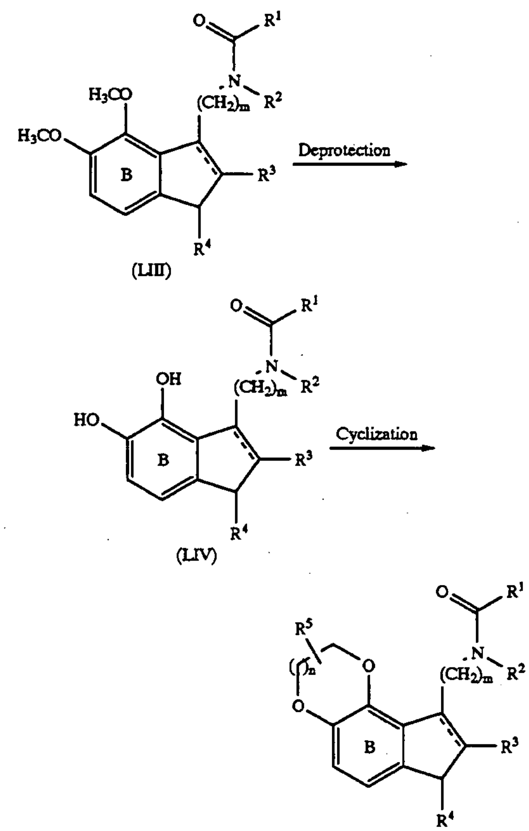
The sulfonate compound can be produced by allowing compound (LII) to react with as a corresponding sulfonyl chloride compound (e.g. benzenesulfonyl chloride, toluenesulfonyl chloride, and C_{1-4} alkylsulfonyl chloride such as methanesulfonyl chloride), in the presence of a base. Relative to 1 mol. of compound (LII), about 1.0 to 50.0 mol., preferably about 1.0 to 20.0 mol., of a sulfonyl chloride compound is employed. Examples of the base includes basic salts such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amine such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyl disilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide and potassium tertiary butoxide, etc. Relative to 1 mol. of compound (LII), the base is used in an amount of about 1.0 to 10.0 mol., preferably about 1.0 to 3.0 mol. Use of a solvent inert to the reaction is advantageous for conducting this reaction. As the solvent, while any one can be used so long as the reaction proceeds, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethyl sulfoxide, etc.; or a mixture of them are preferable. The reaction time is usually 10 minutes to 6 hours, preferably 10 minutes to 2 hours. The reaction temperature is usually −78 to 150° C., preferably −30 to 30° C. While the sulfonate compound thus obtained can be used for the subsequent reaction as in the state of the reaction mixture or as a crude product, it can be

isolated from the reaction mixture by a conventional method and readily purified by means of recrystallization, distillation and chromatography.

The halogenate can be produced by allowing compound (LII) to react with a halogenating agent. Examples of the halogenating agent include phosphohalogenide such as phosphorus trichloride, phosphorus oxychloride and phosphorus tribromide, halogen, and thionyl chloride. Relative to 1 mol. of compound (LII), about 1.0 to 100 mol., preferably about 1.0 to 10 mol. of the halogenating agent is used. It is advantageous to conduct this reaction in the absence of solvent or in the presence of an inert solvent. As the solvent, any one can be used so long as the reaction proceeds, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethyl sulfoxide, etc.; or a mixture of them are preferable. The reaction time ranges usually from 10 minutes to 24 hours, preferably from 30 minutes to 12 hours. The reaction temperature ranges usually from 0 to 200° C., preferably from 10 to 100° C. While the halogenide thus obtained can be used for the subsequent reaction in the state of the reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method, which can readily be purified by means of, for example, recrystallization, distillation and chromatography.

Compound (Ia) is produced by subjecting the sulfonate compound or halogenide thus obtained to ringclosure reaction in the presence of a base. Examples of the base include inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyl dimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyl disilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tertiary butoxide, etc. Relative to 1 mol. of the sulfonate compound or the halogenide, about 1.0 to 50 mol., preferably about 1.0 to 10 mol. of the base is used. This reaction is conducted advantageously using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper the proceeding of the reaction, preferable examples include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; esters such as ethylacetate, etc.; sulfoxides such as dimethyl sulfoxide, etc.; water or a mixture of them. The reaction time is usually 10 minutes to 6 hours, preferably 10 minutes to 2 hours. The reaction temperature is usually 0 to 250° C., preferably 10 to 120° C. The product (Ia) can be isolated from the reaction mixture by a conventional method and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

Reaction Process 7:



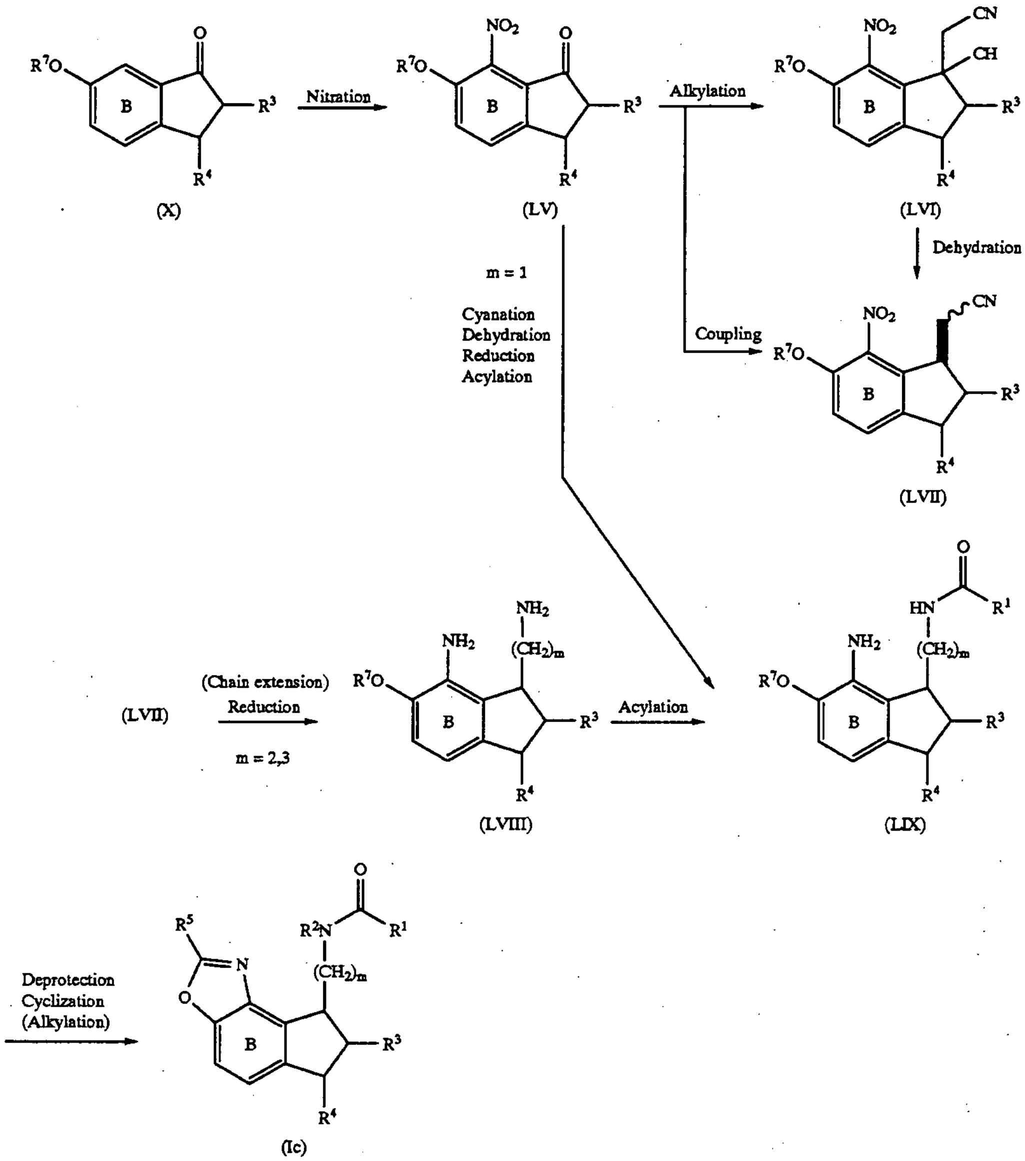
(LIII) (LIV) (Ib)

Compound (LIII) can be produced by a per se known method, for example, methods described in J. Chem. Soc. p.548 (1927), Tetrahedron, Vol.25, p.5475 (1969), Vol.34, p.1435 (1978), Vol.39, p.2803 (1983), and Can. J. Chem. Vol.57, p.1598 (1979), or in accordance with methods analogous to them.

Compound (LIV) can be produced by de-protecting the protected hydroxy group in the same manner as in the production of compound (XVIII) from compound (XVII). This de-protection is conducted by generally known processes. For example, referred to is the disclosure in Chapter "Protection for Phenols and Catechols" in "Protective Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

Compound (Ib) is produced by conducting ring formation reaction at the diol part of compound (LIV). This process is conducted in accordance with generally known steps, for example, methods disclosed in Chapter "Protection for 1,2- and 1,3-diols" in "Protective Groups in Organic Synthesis" by T. W. Green (2nd Ed. 1991), Synthesis p.839 (1986), Tetrahedron Letters, Vol.32, p.2461 (1991), Vol.33, p.4165 (1992), J. Heterocyclic Chem. Vol.26, p.193 (1989) or methods analogous to them.

Reaction Process 8:



Compound (LV) is produced by subjecting compound (X) to nitration. For example, the nitration can be conducted in accordance with "Shin Jikken Kagaku Koza Vol.14, —Synthesis and Reaction of Organic Compounds (III), Chapter of "7 N-containing compounds" (Compiled by The Chemical Society of Japan). To state concretely, (1) synthesis using mixed acids of nitric acid and sulfuric acid, (2) synthesis using acetyl nitrate, (3) synthesis using nitric acid, (4) synthesis using nitronium trifluoromethanesulfonate and (5) synthesis using nitrate such as sodium nitrate or potassium nitrate with a mineral acid are employed, and, among them, nitration using nitrate and mineral acid is generally employed. In this case, relative to 1 mol. of compound (X), about 0.8 to 3.0 mol., preferably about 1.0 to 2.0 mol., of the nitrate is used. As the mineral acid, sulfuric acid is used in general in an amount of 10 to 2000 weight % of compound (X). This reaction is conducted advantageously using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, usually a mineral acid employed as the catalyst is used also as solvent. The reaction time ranges usually from 5 minutes to 10 hours, preferably from 10 minutes to 3 hours. The reaction temperature ranges usually from -20 to 120° C., preferably from -10 to 20° C. The product (LV) can be isolated from the reaction mixture by a conventional method, and can be purified by means of, for example, recrystallization, distillation and chromatography.

Compound (LVII) can be produced, in the same manner as in the above-mentioned method of producing compound (XII) from compound (X), by allowing carbanion produced by processing acetonitrile with a base to react with compound (LV) to afford compound (LVI), followed by subjecting compound (LVI) to dehydration. Compound (LVII) is obtained as coordination isomer of E- or Z-singly or as a mixture of E- and Z-compounds. Relative to 1 mol. of

compound (LV), about 1.0 to 3.0 mol., preferably about 1.0 to 1.3 mol. of acetonitrile is employed. Examples of bases include alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tertiary butoxide, etc. The amount of these bases to be employed ranges from about 1.0 to 5.0 mol., preferably from about 1.0 to 1.5 mol., relative to 1 mol. of compound (LV). It is advantageous that this reaction is conducted using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, use is preferably made of alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; or a mixture of them. The reaction time ranges usually from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature ranges usually from −78 to 100° C., preferably from −78 to 50° C. While the product can be used for the subsequent reaction in the state of reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method, which can readily be purified by means of, for example, recrystallization, distillation and chromatography.

Examples of the catalyst to be used for dehydration include an acid catalyst such as hydrochloric acid, sulfuric acid phosphoric acid, potassium hydrogensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and a boron trifluoride ether complex; and a basic catalyst such as sodium hydroxide and potassium hydroxide, and, further, use may optionally be made of a dehydrating agent such as N,N-cyclohexylcarbodiimide; alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride and methanesulfonyl chloride. This reaction is conducted advantageously in the absence of solvent or using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, preferable examples of the solvents include alcohols such as methanol, ethanol and propanol; ethers such as diethyl ether, tetrahydrofuran, dioxane and 1,2-dimethoxyethane; hydrocarbons such as benzene, toluene, cyclohexane and hexane; amides such as N,N-dimethylformamide and N,N-dimethylacetamide; sulfoxides such as dimethyl sulfoxide; or a mixture of them. The reaction time ranges usually from 30 minutes to 24 hours, preferably from 30 minutes to 5 hours. The reaction temperature ranges usually from 0 to 200° C., preferably from 0 to 150° C.

Compound (LVII) can be produced, in the same manner as in the above-mentioned method of producing compound (XII) from compound (X), by allowing phosphonate carbanion produced by processing alkylsulfonic acid diester with a base to react with compound (LV) to afford stereo isomer of E- or Z-singly or as a mixture of E- and Z-compounds. As alkylsulfonic acid diester, use is made of, for example, diethyl cyanomethyl phosphonate. Relative to 1 mol. of compound (LV), about 1.0 to 3.0 mol., preferably about 1.0 to 1.5 mol. of alkyl phosphonic acid diester is employed. Examples of bases include alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tertiary butoxide, etc. The amount of these bases to be employed ranges from about 1.0 to 5.0 mol., preferably from about 1.0 to 1.5 mol., relative to 1 mol. of compound (LV). It is advantageous that this reaction is conducted using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, use is preferably made of alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; or a mixture of them. The reaction time ranges usually from 1 hour to 50 hours, preferably from 1 hour to 10 hours. The reaction temperature ranges usually from −78 to 200° C., preferably from 0 to 150° C. While the product can be used for the subsequent reaction in the state of reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method, which can readily be purified by means of, for example, recrystallization, distillation and chromatography.

Elongation of the carbon-chain at the side-chain of the compound (LVII) is conducted in accordance with a known reaction for carbon-chain elongation. For example, the cyano group is subjected to hydrolysis under alkaline or acid conditions to convert to carboxyl group, or after leading the carboxyl group to ester, the resultant is subjected to reduction to give an alcohol, followed by halogenation and cyanation.

Compound (LVIII) is produced from compound (LVII), in combination of the same manner as in the below-mentioned reduction of nitro group of compound (LXII) and catalytic hydrogenation using Raney nickel. As the reducing agent, use is made of, for example, metal hydrides such as aluminum hydride and diisobutylaluminum hydride; metal hydride complex compounds such as lithium aluminum hydride and sodium borohydride; or, as catalyst for hydrogenation, use is made of catalysts such as Raney nickel and Raney cobalt; or a suitable combination of them may be resorted to. The amount of a reducing agent, in the case of using a metal hydride for example, ranges from about 1.0 to 10 mol., preferably from about 1.0 to 3.0 mol., relative to 1 mol. of compound (LVII), and, in the case of using a metal hydride complex compounds, its amount ranges, relative to 1 mol. of compound (LVII), from about 1.0 to 10 mol., preferably from about 1.0 to 3.0 mol., and, in the case of hydrogenation, the amount of a catalyst, e.g. Raney nickel or Raney cobalt, ranges from about 10 to 1000 weight %, preferably from about 80 to 300 weight %, relative to compound (LVII). It is advantageous to conduct this reaction by using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, preferable examples include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; and a mixture of these solvents. In the case of using a Raney nickel or Raney cobalt catalyst, amines such as ammonia may further be added optionally to suppress undesirable side reactions. While the reaction times varies with the activity and amount of the reagent then employed, it ranges usually from one hour to 100 hours, preferably from one hour to 50 hours. The reaction temperature ranges usually from 0 to 120° C., preferably from 20 to 80° C. In the case using a catalyst such

as Raney nickel or Raney cobalt, the hydrogen pressure ranges usually from 1 to 100 atm. While the product (LVIII) can be used for the subsequent reaction as in the state of the reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (LIX) with m=1 can be produced in substantially the same manner as in the above-mentioned production of compound (XVI) from compound (X), namely, compound (LV) is processed with trimethyl silyl cyanide in the presence of a Lewis acid, resulting trimethyl silyloxy group is removed with an acid, then reducing the cyano group and the double bond, followed by acylating the resultant amine compound. As the Lewis acid to be used in the first step, mention is made of, for example, zinc iodide, anhydrous aluminum chloride, anhydrous zinc chloride and anhydrous iron chloride. The amount of these Lewis acids to be employed ranges from about 0.01 to 10 mol., preferably from about 0.01 to 1.0 mol., relative to 1 mol. of compound (LV). This reaction is conducted advantageously in the absence of solvent or in the presence of a solvent inert to the reaction. As the solvent any one can be used so long as it does not hamper proceeding of the reaction, and its preferable examples include ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; or a mixture of these solvents. The reaction time ranges usually from 10 minutes to 12 hours, preferably from 30 minutes to 3 hours. The reaction temperature ranges usually from −10 to 200° C., preferably from −10 to 100° C. While the product can be used for the subsequent reaction in the state of reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method, which can be readily purified by means of, for example, recrystallization, distillation and chromatography. The product is then treated with an acid to remove trimethylsilyloxy group. Preferable examples of the acid include inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphor sulfonic acid, etc.; and boron trifluoride ether complex. The amount of these acids to be used ranges from about 1 to 100 mol., preferably from about 1 to 10 mol., relative to 1 mol. of compound (LV). This reaction is advantageously conducted in the absence of solvent or in the presence of a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, preferable examples include ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethyl sulfoxide, etc.; or a mixture of these solvents. The reaction time ranges usually from 30 minutes to 12 hours, preferably from 30 minutes to 5 hours. The reaction temperature ranges usually from 0 to 200° C., preferably from 20 to 150° C. The reduction of cyano group and the double bond can be conducted under the conditions employed for production of compound (XV) from compound (XII). Subsequent acylation can be conducted under the conditions employed for production of compound (XVII) from compound (XVI). While the product (LIX) can be used for the subsequent reaction in the state of reaction mixture or a crude product, it can be optionally isolated from the reaction mixture in accordance with a conventional method, and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

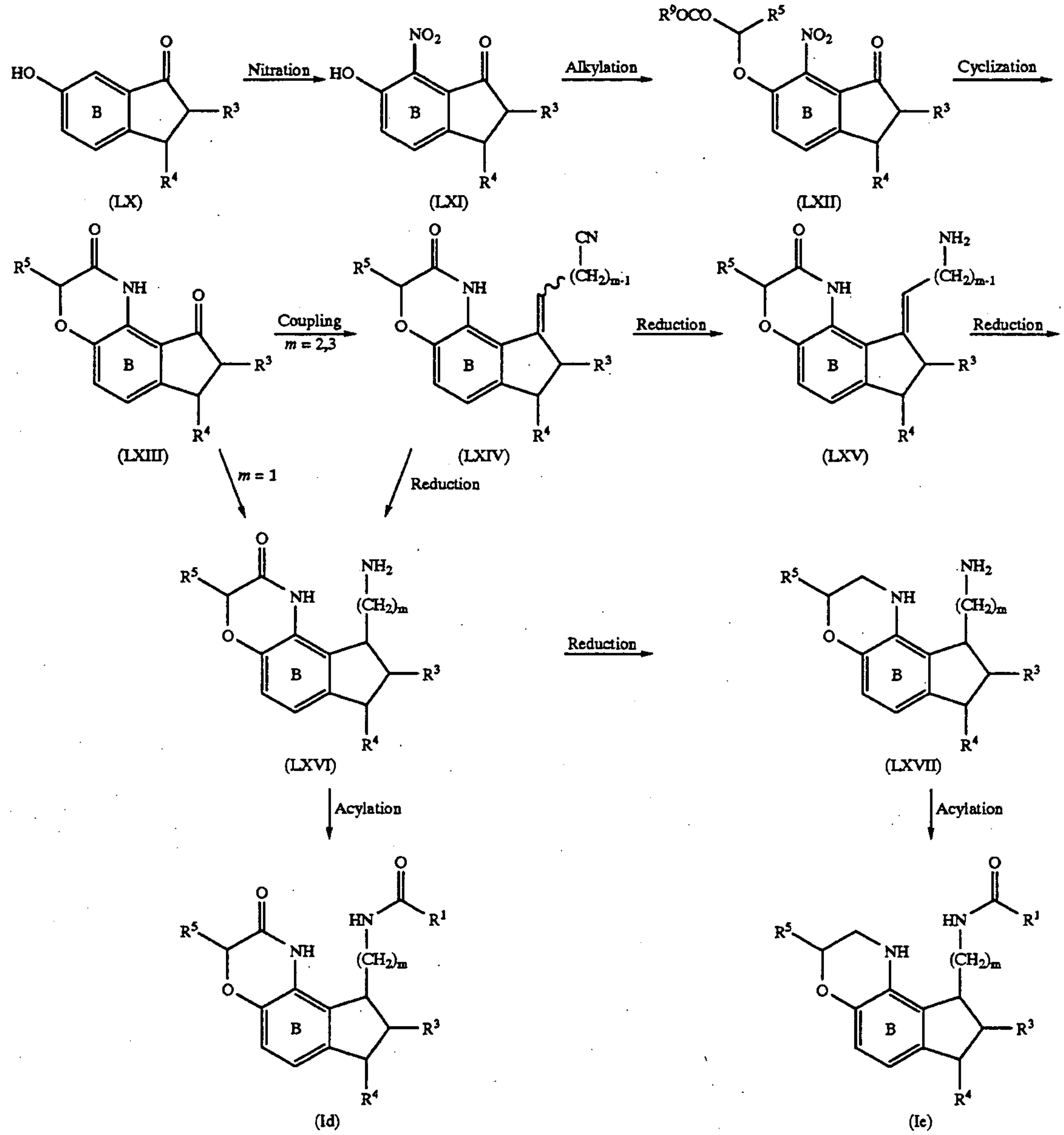
Acylation of compound (LIX) with m=2 or 3 can be conducted under the conditions employed for production of compound (XVII) from compound (XVI). While the product (LIX) can be used for the subsequent reaction in the state of reaction mixture or a crude product, it can be optionally isolated from the reaction mixture in accordance with a conventional method, and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (Ic) is produced by subjecting the protective group R^7 of the phenolic hydroxyl group of compound (LIX) to deprotection followed by allowing cyclization to form an oxazole ring. The deprotection is conducted usually in the presence of an acid catalyst. As the acid, use is made of, for example, a Lewis acid such as boron tribromide or anhydrous aluminum chloride, and a mineral acid such as hydrochloric acid and hydrobromic acid. The amount of these acids to be used ranges from about 0.1 to 100 mol., preferably from about 1 to 10 mol., relative to 1 mol. of compound (LIX). This reaction is advantageously conducted in the absence of solvent or in the presence of a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, its preferable examples include halogenocarbons such as dichloroethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethyl sulfoxide, etc.; water or a mixture solvent of them. The reaction time ranges usually from 30 minutes to 12 hours, preferably from 30 minutes to 5 hours. The reaction temperature ranges usually from −10 to 120° C., preferably from 0 to 80° C. While the product can be used for the subsequent reaction in the state of reaction mixture or a crude product, it can optionally be isolated from the reaction mixture in accordance with a conventional method, which can be readily purified by means of, for example, recrystallization, distillation and chromatography. The subsequent cyclization reaction can be conducted by a per se known method, for example, methods disclosed in Synth. Commun. Vol.16, p.365 (1986) and Org. Prep. Proc. Int. Vol.22, p.613 (1990) or methods analogous to them.

To state further, compound (Ic) with R^2=alkyl group is produced by, after the above-mentioned cyclization reaction, alkylation in the presence of a base using a corresponding alkylating agent (e.g. alkyl halide or sulfonic acid ester of alcohol). Relative to 1 mol. of compound (1c), about 1.0 to 5.0 mol., preferably about 1.0 to 2.0 mol., of the alkylating agent is employed. Examples of the base include inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; basic salts such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amine such as pyridine and lutidine; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyl dimethylamine, 4-dimethyl aminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methyl morpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropyl amide, lithium hexamethyl disilazide, etc.; and metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tertiary butoxide, etc. Relative to 1 mol. of compound (Ic), about 1.0 to 5.0 mol., preferably about 1.0 to 2.0 mol., of the base is used. This reaction is advantageously conducted by using a sol-

vent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, its preferable examples include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethyl sulfoxide, etc.; or a mixture solvent of them. The reaction time ranges usually from 30 minutes to 48 hours, preferably form 30 minutes to 6 hours. The reaction temperature ranges usually from −20 to 200° C., preferably from −10 to 150° C. The product (Ic) can be isolated from the reaction mixture by a conventional method, which can readily purified by means of, for example, recrystallization, distillation and chromatography.

Reaction Process 9:



The compound (LXI) is produced from compound (LX) and corresponding alkylating agent in substantially the same manner as in the production of compound (LV) from compound (X).

Compound (LXII) is produced from compound (LXI), in substantially the same manner as in production of compound (XX) from compound (XVIII).

Production of compound (LXIII) from compound (LXII) is conducted by subjecting the nitro group of compound (LXII) to reduction of catalytic reduction with a reducing agent, followed by cyclization. The reduction of nitro group

can be conducted by a per se known method described in, for example, "Shin Jikken Kagaku Koza Vol. 15—Oxidation and Reduction (compiled by The Chemical Society of Japan), or methods analogous to them. Concretely to state, as the reducing agent to be employed in the reduction of nitro group, use is made of, for example, metal such as zinc, iron, tin, etc.; metal halide such as stannous chloride, etc.; sulfur compound such as sodium sulfide, sodium hydrosulfide, sodium hydrosulfite, ammonium sulfide, etc.; metal hydride complex such as lithium aluminum hydride, etc.; or use is made of catalysts such as platinum, Raney nickel, Raney cobalt, platinum black, palladium carbon, rhodium alumina. The amount of the reducing agent, in the case of using metal hydride complex for example, ranges from about 1.0 to 10.0 mol., preferably from about 1.0 to 3.0 mol., relative to 1 mol. of compound (LXII), and, in the case of hydrogenation, the amount of catalyst ranges from about 10 to 1000 weight %, preferably 80 to 300 weight %, relative to compound (LXII). It is advantageous to condust this reaction by using a solvent inert to the reaction. As the solvent, while any one can be used so long as it does not hamper proceeding of the reaction, preferable examples include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; and a mixture of these solvents. While the reaction times varies with the activity and amount of the reagent then employed, it ranges usually from one hour to 100 hours, preferably from one hour to 50 hours. The reaction temperature ranges usually from 0 to 120° C., preferably from 20 to 80° C. In the case using a catalyst such as Raney nicket or palladium carbon the hydrogen pressure ranges usually from 1 to 100 atm. While the product can be used for the subsequent reaction as in the state of the reaction mixture or as a crude product, it can be isolated from the reaction mixture by a conventional method and can be readily purified by means of, for example, recrystallization, distillation and chromatography. The cyclization is conducted under heating or in the presence of a basic catalyst. Examples of the base as the catalyst include metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tertiary butoxide, etc.; metal hydrides such as sodium hydride, potassium hydride, etc.; lithium reagents such as butyl lithium, phenyl lithium, etc.; and Grignard reagents such as methyl magnesium bromide, phenyl magnesium bromide, etc.; and the amount ranges usually from 0.01 to 5 equivalents, preferably from 0.05 to 0.5 equivalents. This reaction is conducted advantageously in the presence of an solvent inert to the reaction. As the solvent, any one can be used so long as it does not hamper proceeding of the reaction, and its preferable examples include alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; and sulfoxides such as dimethyl sulfoxide, etc.; or a mixture solvent of them. The reaction time ranges usually from 30 minutes to 48 hours, preferably from 30 minutes to 12 hours. The reaction temperature ranges usually from −20 to 200° C., preferably from −10 to 150° C. The product (LXIII) can optionally be isolated from the reaction mixture and can be readily purified by means of, for example, recrystallization, distillation and chromatography.

Compound (LXIV) is produced from compound (LXIII) in substantially the same manner as in the production of compound (XII) from compound (X).

Elongation of carbon chain at the side chain of compound (LXIV) can be conducted in a manner analogous to known carbon-chain elongation reactions, for example, cyano group is hydrolized under alkaline or acid conditions to lead to carboxyl group, or leading the carboxyl group to an ester compound, which is then subjected to reduction to lead to an alcohol compound, followed by halogenation and cyanation.

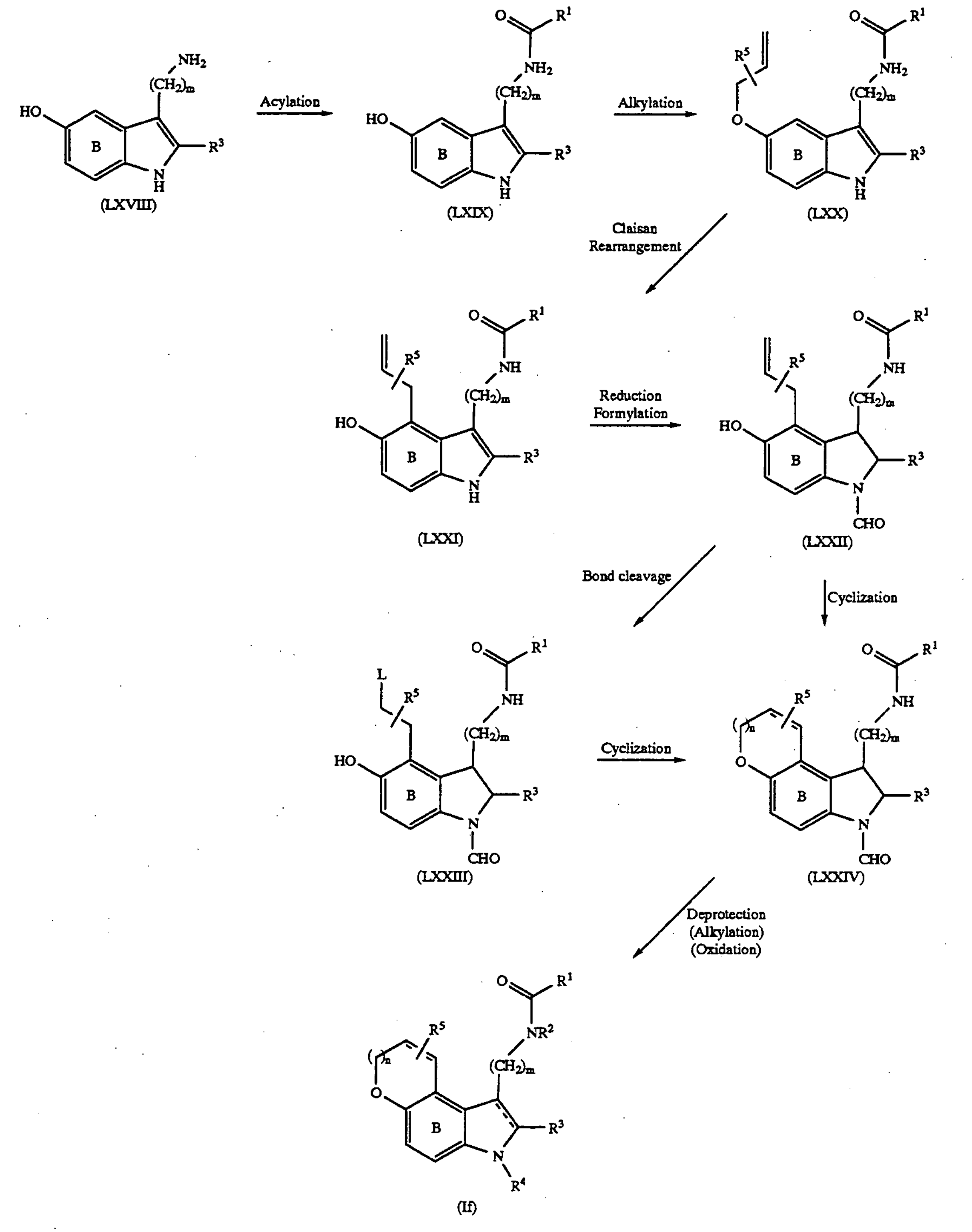
Compound (LXV) is produced from compound (LXIV), in substantially the same manner as in the production of compound (XV) from compound (XII). Compound (LXVI) is produced from compound (LXV) by catalytic hydrogenation. And, compound (LXVI) can be produced directly from compound (LXIV), by employing stronger reaction conditions for producing compound (LXV).

Compound (LXVII) is produced by subjecting the amido moiety of compound (LXVI) to reduction. As the reducing agent, use is made of a metal hydride complex compound (e.g. lithium aluminum hydride). Usually, as the solvent, use is made of ethers such as diethyl ether, tetrahydrofuran, etc.; or a mixture of such ether with an inert solvent (e.g. hexane, cyclohexane, etc.). The amount of the reducing agent to be employed for the reaction ranges usually from 1 to 30 equivalents, preferably from 3 to 10 equivalents. The reaction temperature ranges from −20 to 150° C., preferably from 10 to 100° C. The product (LXVII) can optionally be isolated from the reaction mixture, which can readily be purified by means of, for example, recrystallization, distillation and chromatography.

Compounds (Id) and (Ie) can be produced respectively from compounds (LXVI) and (LXVII) in substantially the same manner as in the production of compound (XVII) from compound (XVI).

Compound (LXIX) can be produced from compound (LXVIII) in substantially the same manner as in the production of compound (XVII) from compound (XVI).

Reaction Process 10:



Compound (LXVIII) can be produced using per se known methods or obtained commercially such as serotonin or its salt.

Compound (LXX) can be produced from compound (LXIX) in substantially the same manner in the production of compound (L) from compound (XVIII).

Compound (LXXI) can be produced from compound (LXX) in substantially the same manner in the production of compound (LI) from compound (L).

Compound (LXXII) can be produced by subjecting compound (LXXI) to reduction, then, by subjecting the resultant to formylation. As the reducing agent, a metal hydride complex compound such as sodium cyano borohydride is

commonly employed. As the solvent, use is made of, usually, an organic acid such as acetic acid and propionic acid or a mixture of the organic acid with an inert solvent (e.g. ethers such as diethyl ether, tetrahydrofuran, etc.; and hydrocarbons such as hexane, cyclohexane, etc.). The amount of the reducing agent to be employed for the reaction ranges usually from 1 to 30 equivalents, preferably from 3 to 10 equivalents. The reaction temperature ranges from −20 to 100° C., preferably from 0 to 80° C. The reaction time ranges usually from 30 minutes to 12 hours, preferably from 30 minutes to 3 hours. The subsequent formylation may be conducted in accordance with the conditions described in, for example, the chapter "Protection for the Amino Group" of "Protective Groups in Organic Synthesis" (2nd Ed., 1991), T. W.Green. The product (LXXII) can optionally be isolated from the reaction mixture by a conventional method, which can readily be purified by means of, for example recrystallization, distillation and chromatography.

The compound (LXXIII) can be produced from compound (LXXII) in substantially the same manner as inn the production of compound (LII) from compound (LI).

The compound (LXXIV) can be produced from compound (LXXIII) in substantially the same manner as in the production of compound (Ia) from compound (LII).

Compound (LXXIV) can be obtained using per se known methods, for example, cyclization reaction using acid catalyst (e.g., hydrochloric acid, sulfuric acid, BF_3 etherate, etc.), peracid (e.g., m-chloroperbenzoic acid, etc.) or halogen (e.g., iodine, bromine, etc.).

Compound (If) can be produced by removing the formyl group of compound (LXXIV) in the presence of an acid catalyst or a basic catalyst. As the reaction conditions for removing the formyl group, reference is made to the description in the Chapter "Protection for the Amino Group" of "Protective Groups in Organic Synthesis" (2nd Ed., 1991) T. W.Green.

And, when desired, alkylation or oxidation to indole from indoline may be conducted.

Just after their isomerization, the configurational isomers (E- and Z forms) of the above-mentioned compounds (XII), (XV), (XXXIV), (XXXV), (LVII), (LXIV) or (LXV) can be isolated and purified by per se means of separation, for example, extraction, recrystallization, distillation, chromatography or the like to obtain pure compounds. If desired, the isomerization of the double-bond moiety in these compounds may be conducted by means of the methods described in "Shin Jikken Kagaku Koza (New Lectures on Experimental Chemistry)" Vol. 14 (edited by Japan Chemical Society), pp. 251–253; "Jikken Kagaku Koza (Lectures on Experimental Chemistry 19)", 4th Ed., pp. 273–274 (edited by the Japan Chemical Society), or methods analogous thereto, for example, methods, under heating, using an acid catalyst, a transition metal catalyst, a metal catalyst, a radical catalyst or a strong base catalyst or a light irradiation to obtain the corresponding pure isomers.

Compound (I) includes stereoisomers, depending on the substituents therein. The present invention encompasses not only single isomers but also mixtures of these.

If desired, any of the above-mentioned reaction steps may be accompanied by known de-protection, acylation, alkylation, hydrogenation, oxidation, reduction, carbon-chain extension and substituent-exchange reaction, either singly or in a combination of two or more of such reactions, to obtain compound (I). For these reactions, for example, referred to are the methods described in "Shin Jikken Kagaku Koza (New lectures on Experimental Chemistry)", Vols. 14 and 15 (edited by Japan Chemical Society, published in 1977, 1978) or methods analogous thereto.

In the above-mentioned reaction steps for producing the compounds of the present invention and those for producing the starting compounds for the compounds of the invention, in the case where the starting compounds for these have, as substituents, an amino group, carboxyl group and/or hydroxy group, these groups may be protected by ordinary protective groups such as those generally employed in peptide chemistry. After the reaction, the protective groups may be removed to obtain the intended products.

The amino-protective group includes, for example, formyl group, C_{1-6} alkyl-carbonyl groups (e.g., acetyl, propionyl, etc.), C_{1-6} alkyloxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, etc.), C_{6-10} arylcarbonyl groups (e.g., benzoyl group, etc.), C_{7-11} aralkyl-carbonyl groups (e.g., benzylcarbonyl, etc.), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, etc. These protective groups may optionally be substituted by one to three substituents such as halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.) and a nitro group.

The carboxyl-protective group includes, for example, C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{6-10} aryl group (e.g., phenyl group, etc.) trityl group, silyl group, etc. These protective groups may optionally be substituted by one to three substituents such as halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), formyl group, C_{1-6} alkyl-carbonyl groups (e.g., acetyl propionyl, butylcarbonyl, etc.) and nitro group.

The hydroxy-protective group includes, for example, C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{6-10} aryl group (e.g., phenyl group, etc.), C_{7-11} aralkyl groups (e.g., benzyl group, etc.), C_{1-6} alkyl-carbonyl groups (e.g., acetyl, propionyl, etc.), C_{6-10} aryl carbonyl group (e.g., benzoyl group, etc.), C_{7-11} aralkyl-carbonyl groups (e.g., benzylcarbonyl, etc.), tetrahydropyranyl group, tetrahydrofuranyl group, silyl group, etc. These protective groups may optionally be substituted by one to three substituents such as halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, etc.), C_{6-10} aryl carbonyl group (e.g., phenyl group), C_{7-11} aralkyl groups (e.g., benzyl, etc.) and nitro group.

These protective groups may be removed by per se known methods or the methods analogous thereto. For example, employable is a reduction or a method using an acid, a base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride or palladium acetate.

The compound (I) of the present invention can be isolated and purified in accordacne with known means, for example, solvent extraction, liquid conversion, solvent transfer, crystallization, recrystallization or chromatography. The starting compounds and their salts for the compound (I) of the invention can also be isolated and purified by known method such as those mentioned above but, as the case may be, they can be directly used in the next reaction step without being isolated.

In the case where the compound (I) is purified by recrystallization, for example, employable are water, alcohols (e.g., methanol, ethanol, n-propanol, iso-propanol, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), nitriles (e.g., acetonitrile, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl

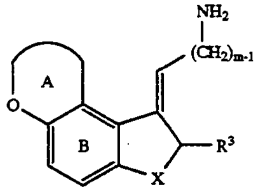
acetate, etc.), carboxylic acids (e.g., acetic acid, propionic acid, etc.), etc. These can be used singly or, if desired, as mixtures comprising two or more at suitable ratios, for example, at 1/1 to 1/10.

In the case where the products are obtained as free compounds in the above-mentioned reaction steps, they can be converted into their salts by per se known methods. In the case where they are obtained as salts, the salts can be converted into free compounds or other salts by ordinary methods. The compound (I) thus obtained can be isolated and purified from the reaction mixtures by known means, for example, solvent transfer, concentration, solvent extraction, fractionating distillation, crystallization, recrystallization or chromatography.

Where the compound (I) exist as configurational isomers, diastereomers or conformers, it can be isolated separately, if desired, in accordance with the above-mentioned means of separation and purification. Mixtures of optically-active compound (I) can be isolated into (+)-form and (−)-form by means of ordinary optical resolution.

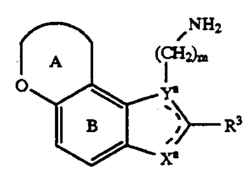
The compound of the formula (i)

(A)



wherein the symbols are as defined above, or (ii)

(A')



wherein the symbols are as defined above, or a salt thereof, as obtained in the reaction processes for the production of the above-mentioned compound (I) is novel compound and can be used as a starting material for the production of the compound of the present invention. Among them, the following are preferred:

2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethylamine,

2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine, and salts of these.

The compound (I) of the present invention shows a high binding affinity for melatonin receptor and compound (I) is highly selective especially in ML-1 receptor. The compound has low toxicity, while having few side effects, and is therefore useful in medicines.

The compound (I) of the present invention acts as melatonin agonists in mammals (e.g., mouse, rat, hamster, rabbit, feline, canine, bovine, sheep, monkey, human, etc.) and is useful as a composition with a binding affinity for melatonin receptor, especially composition agonistic towards melatonin receptor, and, therefore, it can be used for preventing and curing biorhythmic control disorders and various other disorders that may be affected by melatonin, for example, sleep-awake rhythm disorders, jet-lag, shift-work syndrome, seasonal melancholia, genital and neuroendocrine disorders,

senile dementia, Alzheimer's disease, various disorders accompanied by aging (e.g., for preventing aging, etc.), cerebrovascular disorders (e.g., cerebral hemorrhage, etc.), cranial injury, spinal injury, stress, epilepsy, convulsions, anxiety, depression, Parkinsonism, hypertension, glaucoma, cancer, insomnia and diabetes. It is also acts as melatonin antagonists in mammals. In addition, it is also effective for immunoregulation, nootropic, tranquilization and ovulatory regulation (e.g., contraception). The compound (I) of the present invention can be used, for example, in biorhythm regulators, preferably medicines for sleep disorder (e.g., sleep-inducing medicines, etc.), sleep-awake rhythm regulators (including those for controlling sleep-awake rhythm), medicines for physiological syndromes caused by time-zone changes, for example, so-called jet-lag, etc.

The compound (I) of the present invention has low toxicity and can be administered safely through peroral or parenteral routes (e.g., for local administration, rectal administration, intravenous administration, etc.), either directly or as pharmaceutical compositions to be mixed with pharmaceutically acceptable carriers by using per se known methods, for example, as tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, plasters and also as chewing gum, etc. The amount of the compound (I) in the composition of the present invention is approximately 0.01 to nearly 100% by weight of the total weight of the composition. The dose of the composition varies, depending on the subject to which the composition is administered, the administration route, the disorder, etc. For example, when the composition is administered to an adult patient suffering from sleep disorders, it is preferable to administer once daily or severally divided dosages in an amount of approximately 0.0005 to 2 mg/kg body weight, preferably approximately 0.001 to 1 mg/kg body weight, more preferably approximately 0.001 to 0.5 mg/kg body weight, in terms of the amount of the active ingredient, compound (I). The composition may be used with other active ingredients (e.g., benzodiazepine-type medicines comprising benzodiazepine compounds such as triazolam, diazepam, alprazolam, estazolam, etc.; regulating agents of sleep rhythm comprising fatty acid derivatives such as butoctamide and its salt, etc.; sleep ruducing substances comprising cis-9,10-octadecenamide, etc.) Such other active ingredient and the compound (I) may be mixed by means of per se known methods to give pharmaceutical compositions (e.g., tablets, powders, granules, capsules including soft capsules, liquids, injections, suppositories, sustained release preparations, etc.); or they are separately formulated into different preparations, which may be administered to one and the same subject either simultaneously or at different times.

Pharmaceutically acceptable carriers employable in the production of the composition of the present invention include various organic and inorganic carrier substances which are known to be usable in pharmaceutical compositions. For example, they include excipients, lubricants, binders, disintegrants, etc. in solid compositions; solvents, solubilizers, suspending agents, isotonizing agents, buffers, pain-easing agents, etc. in liquid compositions. If desired, ordinary preservatives, antioxidants, colorants, sweeteners, adsorbents, moisturizers, and other additives may also be employed.

Excipients employable in the present invention include, for example, lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic acid anhydride, etc.

Lubricants include, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, sodium carboxymethyl cellulose, etc.

Disintegrants include, for example, starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium crosscarmellose, sodium carboxymethyl starch, L-hydroxypropyl cellulose, etc.

Solvents include, for example, water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, olive oil, etc.

Solubilizers include, for example, polyethyleneglycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Suspending agents include, for example, surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.

Isotonizing agents include, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

Buffers include, for example, buffer liquids such as phosphates, acetates, carbonates, citrates, etc.

Pain-easing agents include, for example, benzyl alcohol, etc.

Preservatives include, for example, parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

Antioxidants include, for example, sulfites, ascorbic acid, α-tocopherol, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

Examples

The present invention is described in detail by means of the following reference examples, examples, formulation examples and experimental examples, which, however, serve merely to illustrate the embodiments of the invention but not to restrict the invention. Various modifications and changes can be made in the present invention without departing from the spirit and scope of the invention.

"Room temperature" as referred to in the following reference examples and examples generally indicates a temperature of from about 10° C. to 35° C. Unless otherwise specifically indicated, "%" is percent by weight.

The abbreviations referred to herein are defined as follows:

s: singlet
d: doublet
t: triplet
q: quartet
m: multiplet
br: broad
J: coupling constant
Hz: hertz
$CDCl_3$: deuterochloroform
d_6-DMSO: (dimethylsulfoxide)-d_6
D_2O: deuterium oxide
NMR: proton nuclear magnetic resonance
BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
T-BINAP: 2,2'-bis[di(4-methylphenyl)phosphino]-1,1'-binaphthyl
DM-BINAP: 2,2'-bis[di(3,5-dimethylphenyl)-phosphino]-1,1'-binaphthyl

Reference Example 1

2,3-Dihydrobenzofuran-5-carbaldehyde

Titanium chloride (28 ml) was dropwise added to a dichloromethane (100 ml) solution containing 2,3-dihydrobenzofuran (10.0 g, 83.2 mmols) and dichloromethyl methyl ether (11.3 ml, 0.125 mmols), while cooling with ice. The mixture was stirred for 1 hour, while still cooling with ice, and then water was added thereto. Dichloromethane was removed under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel chromatography (hexane/ethyl acetate=1/1) to obtain 11.4 g (yield: 92%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 3.28 (2H, t, J=8.8 Hz), 4.70 (2H, t, J=8.8 Hz), 6.88 (1H, d, J=8.4 Hz), 7.67 (1H, dd, J=1.0 Hz, 8.4 Hz), 7.75 (1H, d, J=1.0 Hz), 9.83 (1H, s)

Reference Example 2

Ethyl (E)-3-(2,3-dihydrobenzofuran-5-yl)- 2-propenoate

60% sodium hydride (3.39 g, 84.6 mmols) was added to a tetrahydrofuran (150 ml) solution of triethyl phosphonoacetate (19.0 g, 84.6 mmols) while cooling with ice, and the mixture was stirred for 20 minutes. To this was dropwise added a tetrahydrofuran (15 ml) solution of 2,3-dihydrobenzofuran-5-carbaldehyde (11.4 g, 76.9 mmols) and stirred further for 1 hour. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate=from 95/5 to 9/1) to obtain 14.7 g (yield: 88%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz), 3.23 (2H, t, J=8.8 Hz), 4.25 (2H, q, J=7.2 Hz), 4.63 (2H, t, J=8.8 Hz), 6.28 (1H, d, J=16.0 Hz), 6.79 (1H, d, J=8.4 Hz), 7.31 (1H, d, J=8.4 Hz), 7.41 (1H, s), 7.64 (1H, d, J=16.0 Hz)

Reference Example 3

Ethyl 3-(2,3-Dihydrobenzofuran-5-yl)propionate

5% Palladium-carbon (1 g, containing 50% water) was added to an ethanol (150 ml) solution of ethyl (E)-3-(2.3-dihydrobenzofuran-5-yl)-2-propenoate (14.7 g, 66.7 mmols), and the mixture was stirred in a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 14.6 g (yield: 99%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.2 Hz), 2.57 (2H, t, J=7.8 Hz), 2.88 (2H, t, J=7.8 Hz), 3.18 (2H, t, J=8.6 Hz), 4.13 (2H, q, J=7.2 Hz), 4.55 (2H, t, J=8.6 Hz), 6.70 (1H, d, J=8.2 Hz), 6.94 (1H, d, J=8.2 Hz), 7.05 (1H, s);

The compound obtained herein was used in the next reaction without being further purified.

Reference Example 4

Ethyl 3-(7-Bromo-2,3-dihydrobenzofuran-5-yl) propionate

Bromine (10.5 g, 65.8 mmols) was dropwise added to an acetic acid (150 ml) solution containing ethyl 3-(2,3-dihydrobenzofuran-5-yl)propionate (14.5 g, 65.8 mmols) and sodium acetate (5.94 g, 72.4 mmols), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Water was added to the residue, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution and then dried with anhydrous magnesium sulfate. This was concentrated under reduced pressure to obtain 19.2 g (yield: 97%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.2 Hz), 2.57 (2H, t, J=7.6 Hz), 2.85 (2H, t, J=7.6 Hz), 3.28 (2H, t, J=8.8 Hz), 4.13 (2H, q, J=7.2 Hz), 4.65 (2H, t, J=8.8 Hz), 6.97 (1H, s), 7.11 (1H, s);

The compound obtained herein was used in the next reaction without being further purified.

Reference Example 5

3-(7-Bromo-2,3-dihydrobenzofuran-5-yl)propionic Acid

An aqueous solution (100 ml) of sodium hydroxide (15 g) was added to a tetrahydrofuran (20 ml) solution of ethyl 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)propionate (19.1 g, 63.8 mmols), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was made acidic with hydrochloric acid added thereto, and this was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to obtain 12.8 g (yield: 73%) of the target compound.

m.p.: 117-118° C.; NMR ($CDCl_3$) δ: 2.64 (2H, t, J=7.4 Hz), 2.87 (2H, t, J=7.4 Hz), 3.82 (2H, t, J=8.8 Hz), 4.65 (2H, t, J=8.8 Hz), 6.97 (1H, s), 7.11 (1H, s), hidden (1H)

Reference Example 6

4-Bromo-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Thionyl chloride (10.1 ml, 0.139 mols) was added to 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)propionic acid (12.7 g, 46.2 mmols), the mixture was stirred at 75° C. for 30 minutes, and the reaction mixture was then concentrated under reduced pressure to obtain an acid chloride. The thus-prepared acid chloride was dropwise added to a 1,2-dichloroethane (100 ml) suspension of anhydrous aluminium chloride (6.77 g, 50.8 mmols) while cooling with ice, and the mixture was stirred for 30 minutes. The reaction mixture was poured into water and then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate=8.2) and then recrystallized from ethyl acetate/isopropyl ether to obtain 1.00 g (yield: 9%) of the target compound.

m.p.: 149–150° C.; NMR ($CDCl_3$) 6: 2.64–2.72 (2H, m), 3.08 (2H, t, J=5.8 Hz), 3.57 (2H, t, J=9.0 Hz), 4.76 (2H, t, J=9.0 Hz), 7.41–7.43 (1H, m)

Reference Example 7

(E)-(4-bromo-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile

60% Sodium hydride (0.17 g, 4.35 mmols) was added to a tetrahydrofuran (20 ml) solution of diethyl cyanomethylphosphonate (0.77 g, 4.35 mmols) while cooling with ice, and the mixture was stirred for 20 minutes. To this was added a tetrahydrofuran (10 ml) solution of 4-bromo-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one (1.00 g, 3.95 mmols), and the mixture was stirred at room temperature further for 2 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate=from 85/15 to 8/2) and then recrystallized from ethyl acetate/isopropyl ether to obtain 0.47 g (yield: 43%) of the target compound.

m.p.: 200–203° C.; NMR ($CDCl_3$) δ: 3.02–3.18 (4H, m), 3.41 (2H, t, J=8.8 Hz), 4.77 (2H, t, J=8.8 Hz), 5.42–5.46 (1H, m), 7.31 (1H, s)

Reference Example 8

3-(3-Fluoro-4-methoxyphenyl)propionic Acid

Malonic acid (7.5 g, 72.1 mmols) and piperidine (0.84 g, 9.83 mmols) were added to a pyridine (20 ml) solution of 3-fluoro-4-methoxybenzaldehyde (10.1 g, 65.5 mmols), and the mixture was stirred under heat at 120° C. for 7 hours. The reaction mixture was poured into water containing ice, and the powder that precipitated was taken out through filtration. The powder was dried and dissolved in acetic acid (300 ml) without being further purified. To this was added 5% palladium-carbon (3 g, containing 50% water), and the mixture was stirred in a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 8.54 g (yield: 66%) of the target compound.

m.p.: 114–117° C.; NMR ($CDCl_3$) δ: 2.65 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 3.87 (3H, s), 6.80–7.00 (3H, m), hidden (1H)

Reference Example 9

5-Fluoro-6-methoxy-1-indanone

In the same manner as in Reference Example 6, the target compound was obtained from 3-(3-fluoro-4-methoxyphenyl)propionic acid. The yield was 91%.

m.p.: 152–153° C. (recrystallized from methanol/ethyl acetate); NMR ($CDCl_3$) δ: 2.71 (2H, t, J=5.7 Hz), 3.08 (2H, t, J=5.7 Hz), 3.92 (3H, s), 7.17 (1H, d, J=10.3 Hz), 7.29 (d, J=8.1 Hz); Elemental Analysis for $C_{10}H_9FO_2$: Calcd.: C 66.66; H 5.03; Found: C 66.82; H 5.06

Reference Example 10

(E)-(5-fluoro-6-methoxyindan-1-ylidene) acetonitrile

In the same manner as in Reference Example 7, the target compound was obtained from 5-fluoro-6-methoxy-1-indanone and diethyl cyanomethylphosphonate. The yield was 75%.

m.p.: 197–199° C. (recrystallized from hexane/ethyl acetate); NMR ($CDCl_3$) δ: 3.00–3.19 (4H, m), 3.92 (3H, s), 5.53 (1H, t, J=2.2 Hz), 7.02 (1H, d, J=7.6 Hz), 7.07 (1H, d, J=10.3 Hz); Elemental Analysis for $C_{12}H_{10}FNO$: Calcd.: C 70.93; H 4.96; N 6.89; Found: C 70.65; H 5.13; N 6.99

Reference Example 11

2-(5-Fluoro-6-methoxyindan-1-yl)ethylamine

In the same manner as in Example 18 to be mentioned later herein, the target compound was obtained from (E)-(5-fluoro-6-methoxyindan-1-ylidene)acetonitrile. The yield was 88%. The compound was oily.

NMR ($CDCl_3$) δ: 1.50–1.80 (2H, m), 1.90–2.08 (1H, m), 2.20–2.40 (1H, m), 2.67–2.90 (4H, m), 3.00–3.20 (1H, m), 3.87 (3H, s), 6.80 (1H, d, J=8.1 Hz), 6.92 (1H, d, J=11.0 Hz), hidden (2H)

Reference Example 12

N-[2-(5-fluoro-6-methoxyindan-1-yl)ethyl) propionamide

Propionyl chloride (2.5 g, 27.0 mmols) was gradually and dropwise added to a tetrahydrofuran (20 ml) solution containing 2-(5-fluoro-6-methoxyindan-1-yl)ethylamine (4.35 g, 20.8 mmols) and triethylamine (4.21 g, 41.6 mmols) while cooling with ice. After having been stirred at room temperature for 2 hours, the reaction mixture was poured into water, and the organic substance was extracted out with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate/hexane=90/10) to obtain 4.87 g (yield: 88%) of the target compound.

m.p.: 76–78° C.; NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.7 Hz), 1.47–1.81 (2H, m), 1.94–2.41 (2H, m), 2.21 (2H, q, J=7.7 Hz), 2.70–2.90 (2H, m), 3.00–3.20 (1H, m), 3.38 (2H, q, J=7.3 Hz), 3.87 (3H, s), 5.50 (1H, br s), 6.82 (1H, d, J=8.1 Hz), 6.92 (1H, d, J=11.4 Hz); Elemental Analysis for $C_{15}H_{20}NFO_2$: Calcd.: C 67.90; H 7.60; N 5.28; Found: C 67.83; H 7.27; N 5.25

Reference Example 13

N-[2-(5-fluoro-6-hydroxyindan-1-yl)ethyl]propionamide

Boron tribromide (7.9 g, 31.5 mmols) was gradually and dropwise added to a dichloromethane (100 ml) solution of N-[2-(5-fluoro-6-methoxyindan-1-yl)ethyl]propionamide (4.18 g, 15.8 mmols) while cooling with ice. After having been stirred for 2 hours while still cooling with ice, the reaction mixture was poured into water containing ice and then stirred at room temperature for 3 hours, and the organic substance was extracted with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate/hexane=9/1) to obtain 3.68 g (yield: 93%) of the target compound.

m.p.: 93–96° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.7 Hz), 1.47–1.80 (2H, m), 1.88–2.10 (1H, m), 2.22 (2H, q, J=7.7 Hz), 2.20–2.40 (1H, m), 2.65–2.90 (2H, m), 2.95–3.13 (1H, m), 3.37 (2H, q, J=7.5 Hz), 5.59 (1H, br s), 6.09 (1H, br s), 6.83 (1H, d, J=8.4 Hz), 6.89 (1H, d, J=10.6 Hz); Elemental Analysis for $C_{14}H_{18}NFO_2$: Calcd.: C 66.91; H 7.22; N 5.57; Found: C 66.84; H 7.10; N 5.54

Reference Example 14

N-(2-(5-fluoro-6-(2-propynyloxy)indan-1-yl)ethyl] propionamide

Potassium carbonate (1.37 g, 9.95 mmols) and propargyl bromide (2.4 g, 19.9 mmols) were added to a dimethylformamide (10 ml) solution of N-[2-(5-fluoro-6-hydroxyindan-1-yl)ethyl]propionamide (0.5 g, 1.99 mmols) and stirred at 120° C. for 2 hours. The reaction solution was poured into water, and the organic substance was extracted out with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate) to obtain 0.56 g (yield: 97%) of the target compound.

m.p.: 78–81° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.5 Hz), 1.50–1.83 (2H, m), 1.91–2.11 (1H, m), 2.21 (2H, q, J=7.5 Hz), 2.20–2.41 (1H, m), 2.55 (1H, t, J=2.3 Hz), 2.65–2.95 (2H, m), 3.00–3.20 (1H, m), 3.38 (2H, q, J=7.5 Hz), 4.74 (2H, d, J=2.2 Hz), 5.47 (1H, br s), 6.91 (1H, s), 6.96 (1H, s)

Reference Example 15

Ethyl 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl) propionate

Bromine (0.80 g, 5.01 mmol) was added dropwise to a mixture of ethyl 3-(7-bromo-2,3-dihydrobenzofuran-5-yl) propionate (1.0 g, 3.34 mmol) and iron (10 mg) in acetic acid (10 ml) and the reaction mixture was stirred at 50° C. for 5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Water was added to the residue and the organic matter was extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium bicarbonate solution, a saturated aqueous sodium chloride solution and water and then dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:3) to give 0.67 g (yield: 53%) of the target compound.

m.p.: 42–43° C.; NMR (CDCl3) δ: 1.25 (3H, t, J=7.3 Hz), 2.60 (2H, t, J=7.7 Hz), 3.07 (2H, t, J=7.7 Hz), 3.27 (2H, t, J=8.8 Hz), 4.14 (2H, q, J=7.3 Hz), 4.68 (2H, t, J=8.8 Hz), 7.06 (1H, s)

Reference Example 16

3-(6,7-Dibromo-2,3-dihydrobenzofuran-5-yl)propionic acid

In the same manner as in Reference Example 5, the target compound was obtained from ethyl 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)propionate. The yield was 93%.

m.p.: 177–178° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 2.67 (2H, t, J=7.5 Hz), 3.08 (2H, t, J=7.5 Hz), 3.27 (2H, t, J=8.8 Hz), 4.68 (2H, t, J=8.8 Hz), 7.07 (1H, s)

Reference Example 17

4,5-Dibromo-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

In the same manner as in Reference Example 6, the target compound was obtained from 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)propionic acid. The yield was 88%.

m.p.: 224–226° C. (recrystallized from chloroform/isopropyl ether); NMR ($CDCl_3$) δ: 2.72 (2H, t, J=5.9 Hz), 3.05 (2H, t, J=5.9 Hz), 3.55 (2H, t, J=9.0 Hz), 4.79 (2H, t, J=9.0 Hz)

Reference Example 18

1,2,6,7-Tetrahydro-8H-indeno[5,4-b]furan-8-one

5% Palladium carbon (50% hydrous, 2.9 g) and sodium acetate (17.9 g, 0.22 mol) were added to a solution of 4,5-dibromo-1,2,6,7-tetrahydro- 8H-indeno[5,4-b]furan-8-one (29.0 g, 87.4 mmol) in acetic acid (550 ml), and the mixture was catalytically reduced in a hydrogen atmosphere at ordinary temperature and ordinary pressure. After absorption of the calculated amount of hydrogen, the palladium carbon was filtered off and the solvent was distilled off under reduced pressure. Water was added to the residue and the organic matter was extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium bicarbonate solution, a saturated aqueous sodium chloride solution and water and then dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatogarphy (ethyl acetate:hexane=15:85) to give the target compound. The yield was 13.5 g (89%).

m.p.: 133–134° C. (recrystallized from ethyl acetate/hexane); NMR (CDC13) δ: 2.68 (2H, t, J=5.9 Hz), 3.08 (2H, t, J=5.9 Hz), 3.47 (2H, t, J=8.8 Hz) 4.65 (2H, t, J=8.8 Hz), 7.01 (1H, d, J=8.1 Hz), 7.21 (1H, d, J=8.1 Hz); Elemental Analysis for $C_{11}H_{10}O_2$: Calcd.: C 75.84; H 5.79; Found: C 75.69; H 5.75

Reference Example 19

(E)-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile

In the same manner as in Reference Example 7, the target compound was obtained from 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one and diethyl cyanomethyl-phosphonate. The yield was 60%.

m.p.: 149–151° C. (recrystallized from methanol); NMR ($CDCl_3$) δ: 3.00–3.20 (4H, m), 3.31 (2H, t, J=8.8 Hz), 4.67 (2H, t, J=8.8 Hz) 5.45 (1H, t, J=2.4 Hz), 6.86 (1H, d, J=8.1 Hz), 7.11 (1H, d, J) =8.1 Hz); Elemental Analysis for $C_{13}H_{11}NO$: Calcd.: C 79.17; H 5.62; N, 7.10; Found: C 79.21; H 5.82; N, 7.18

Reference Example 20

(S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl] ethylamine hydrochloride

A Hastelloy autoclave (200 mL) was charged with (E)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene) ethylamine (1.00 g, 5.00 mmol.), Ru_2Cl_4[(R)-BINAP]$_2$NEt$_3$ (21.0 mg) and methanol (10 mL) under nitrogen atmosphere. Into the vessel, hydrogen gas was introduced up to 100 atmospheric pressure. The mixture was stirred for 20 hours at 50° C. The reaction system was depressurized to normal, followed by determination of the conversion and the optical purity of the product, (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine), by means of high performance liquid chromatography. The conversion was 100% and the optical purity was 88.8%e.e.

Toluene (10 mL) was added to the residue (1.02 g) obtained by concentration under reduced pressure. The mixture was cooled on an ice-bath, to which was added, while stirring, 2% hydrochloric acid (10 mL). The reaction mixture was stirred for 30 minutes, which was concentrated under reduced pressure to leave the residue (1.21 g). The concentrate was dissolved in methanol (5 mL), to which was added acetone (10 mL). The mixture was cooled to 0° C., which was then subjected to filtration to collect the title compound (0.64 g). Further, the filtrate was concentrated under reduced pressure. The concentrate (0.34 g) was recrystallized from a mixture of methanol (1.5 mL) and acetone (3.0 mL) to give the title compound (0.17 g, total yield 0.81 g, yield 68%). This hydrochloride was processed with a 5% aqueous solution of sodium hydroxide to give (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine. The optical purity of the product was determined by means of high performance liquid chromatography, which was 100%e.e.

Reference Example 21

(S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl] ethylamine

A Hastelloy autoclave (200 mL) was charged with (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine (0.20 g, 1.00 mmol.), Ru_2Cl4[(R)-BINAP]$_2$NEt$_3$ (0.42 g), methanol (20 mL) and methylene chloride (5 mL) under nitrogen atmosphere. The mixture was heated up to 50° C., followed by introducing hydrogen gas into the vessel up to 50 atmospheric pressure. The reaction mixture was stirred for 15 minutes at 50° C., which was then cooled to room temperature and depressurized to normal pressure. To the reaction mixture was added a solution of (E)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene) ethylamine (20.0 g, 99.4 mmol.) in methanol (30 mL). Into the reaction vessel was again introduced hydrogen gas up to 100 atmospheric pressure. The reaction mixture was stirred for 20 hours at 55° C. The pressure in the vessel was reverted to normal, then the conversion and the optical purity of the product, ((S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine), were determined by means of high performance liquid chromatography. The conversion was 100% and the optical purity of 90.3%e.e.

Reference Example 22

(S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine

A Hastelloy autoclave (100 mL) was charged with (E)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene) ethylamine (0.50 g, 2.50 mmol.), Ru_2Cl_4[(R)-T-BINAP]$_2$NEt$_3$ (5.0 mg) and methanol (5.0 mL) under nitrogen atmosphere, followed by introducing hydrogen gas up to 100 atmospheric pressure. The reaction mixture was stirred for 20 hours at 50° C. The pressure in the vessel was reverted to normal, and the conversion and the optical purity of the product, ((S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4,b]furan-8-yl)ethylamine were determined by means of high performance liquid chromatography. The conversion was 100% and the optical purity was 74.0%e.e.

Reference Examples 23 to 25

Only the catalyst in Reference Example 22 was replaced with Ru(OCOCH$_3$)$_2$[(R)-BINAP], Ru(OCOCH$_3$)$_2$[(R)-T-BINAP] or Ru_2Cl_4[(R)-DM-BINAP]$_2$NEt$_3$, and the hydrogenation was conducted in the same manner as in Reference Example 22 to obtain the following results:

Catalyst	Conversion	Optical purity
R.Ex.23 Ru(OAc)$_2$((R)-BINAP)	100%	75.4% ee
R.Ex.24 Ru(OAc)$_2$((R)-T-BINAP)	100%	74.0% ee
R.Ex.25 Ru_2Cl_4((R)-DM-BINAP)$_2$NEt$_3$	100%	36.4% ee

For the determination of the conversion and the optical purity by means of high performance liquid chromatography in Reference Examples 20 to 25, the following conditions were employed.

High performance liquid chromatography: SHIMAZU SCL-10A

Column: ULTRON ES-OVM (4.6 mm×150 mm, SHINWA CHEMICAL INDUSTRIES LTD.)

Mobile phase: 40 mmol/L KH_2PO_4 aq. sol./ethanol=90/10 (pH=7.5 NaOH)

Wave length: UV 280 nm

Flow rate: 1.0 mL/min.

Reference Example 26

(E)-(6-methoxyindan-1-ylidene)acetonitrile

In substantially the same manner as in Reference Example 7, the title compound was produced from diethyl 6-methoxy-1-indanone and diethyl cyanomethylphosphonate (yield 73%).

m.p.: 92–95° C. (recrystallized from ethyl acetate) NMR ($CDCl_3$) δ: 2.97–3.20 (4H, m), 3.84 (3H, s), 5.61 (1H, t, J=2.6 Hz), 6.95–7.03 (2H, m), 7.26 (1H, dd, J=0.7 & 8.1 Hz); Elemental Analysis for $C_{12}H_{11}NO$: Calcd.: C 77.81; H 5.99; N 7.56; Found: C 77.79; H 6.01; N 7.58

Reference Example 27

(E)-2-(6-methoxyindan-1-ylidene)ethylamine hydrochloride

To a solution of (E)-(6-methoxyindan-1-ylidene) acetonitrile (5.0 g, 27 mmol.) in ethanol (50 mL) were added a saturated ammonia/ethanol solution (250 mL) and Raney cobalt (10 g). The mixture was stirred for 5 hours at room temperature under hydrogen atmosphere (5 kgf/cm^2). The Raney cobalt was filtered off, and the solvent was distilled off under reduced pressure to leave (E)-2-(6-methoxyindan-1-ylidene)ethylamine. This oily residue was dissolved in ethanol (20 mL). The solution was cooled to −40° C., to which was added a saturated hydrogen chloride/ethanol solution. The resulting crystalline precipitate was collected by filtration to obtain the title compound (yield 4.3 g, 71%).

m.p.: 177–179° C.; NMR (d_6-DMSO, D_2O) δ: 2.76–3.00 (4H, m), 3.40–3.65 (2H, m), 3.77 (3H, s), 5.98 (1H, t, J=7.5 Hz), 6.85 (1H, dd, J=2.2 & 8.4 Hz), 7.01 (1H, d, J=2.2 Hz), 7.22 (1H, d, J=8.4 Hz), 8.22 (2H, br s); Elemental Analysis for $C_{12}H_{15}NO.HCl$: Calcd.: C 63.85; H 7.14; N 6.21; Cl 15.71; Found: C 63.53; H 6.85; N 6.16; Cl 15.40

Reference Example 28

(E)-N-[2-(6-methoxyindan-1-ylidene)ethyl] propionamide

In substantially the same manner as in Reference Example 12, the title compound was produced from (E)-2-(6-methoxyindan-1-ylidene)ethylamine and propionyl chloride (yield 78%).

m.p.: 129–131° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.5 Hz), 2.24 (2H, q, J=7.5 Hz), 2.73–2.86 (2H, m), 2.90–3.20 (2H, m), 3.81 (3H, s), 4.04 (2H, t, J=6.2 Hz), 5.55 (1H, br s), 5.88 (1H, m), 6.79 (1H, dd, J=2.4 & 8.1 Hz), 6.93 (1H, d, J=2.4 Hz), 7.14 (1H, d, J=8.1 Hz); Elemental Analysis for $C_{15}H_{19}NO_2$: Calcd.: C 73.44; H 7.81; N 5.71; Found: C 72.91; H 7.81; N 5.58

Reference Example 29

(S)-N-[2-(6-methoxyindan-1-yl)ethyl)propionamide

(E)-N-[2-(6-methoxyindan-1-ylidene)ethyl] propionamide (3.5 g, 14.26 mmol.) and $Ru(OCOCH_3)_2$[(S)-BINAP] (120 mg, 142 μmol. were added to degasified absolute methanol (70 mL). The solution was stirred for 3 hours at 70° C. in an autoclave (hydrogen pressure 90 atm.). The reaction mixture was subjected to analysis by means of chiral column high performance liquid chromatography to find that the asymmetric yield of (S)-N-[2-(6-methoxyindan-1-yl) ethyl]propionamide was 95%e.e, while the chemical yield of it was 99%.

The reaction mixture was concentrated to dryness under reduced pressure. The resulting oily residue was purified by means of a short column chromatography (silica gel 7 g), followed by recrystallization from ethyl acetate/hexane to afford the title compound (yield 2.92 g, 83%), whose optical purity was not lower than 99%e.e. and chemical purity was not lower than 99%.

$[\alpha]_D^{20}$=−7.0° (c 1.000, ethanol); m.p.: 76–77° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=8 Hz), 1.56–1.64 (1H, m), 1.72 (1H, qd, J=8 & 13 Hz), 2.04 (1H, dtd, J=4, 8 & 13 Hz), 2.19 (2H, q, J=8 Hz), 2.32 (1H, dtd, J=4, 8 & 13 Hz), 2.77 (1H, td, J=8 & 16 Hz), 2.85 (1H, dtd, J=4, 8 & 16 Hz), 3.11 (1H, ddt, J=4, 8 & 14 Hz), 3.34 (3H, s), 3.37–3.41 (2H, m), 5.53 (1H, br s), 6.71 (1H, dd, J=2 & 8 Hz), 6.75 (1H, d, J=2 Hz), 7.10 (1H, d, J=8 Hz); Elemental Analysis for $C_{15}H_{21}NO_2$: Calcd.: C 72.84; H 8.56; N 5.66; Found: C 72.59; H 8.50; N 5.84

Reference Example 30

(S)-N-[2-(5-bromo-6-methoxyindan-1-yl)ethyl] propionamide

In substantially the same manner as in Reference Example 4, the title compound was produced from (S)-N-(6-methoxyindan-1-yl)ethyl]propionamide and bromine (yield 86%).

[α]D^{20}=+5.20 (c 1.000, ethanol); m.p.: 105–107° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.7 Hz), 1.49–1.81 (2H, m), 1.98–2.41 (2H, m), 2.21 (2H, q, J=7.7 Hz), 2.69–2.98 (2H, m), 3.00–3.20 (1H, m), 3.39 (2H, q, J=7.3 Hz), 3.88 (3H, s), 5.48 (1H, br s), 6.78 (1H, s), 7.37 (1H, s); Elemental Analysis for $C_{15}H_{20}BrNO_2$: Calcd.: C 55.23; H 6.18; N 4.29; Found: C 55.15; H 6.18; N 4.25

Reference Example 31

(S)-N-[2-(5-bromo-6-hydroxyindan-1-yl)ethyl] propionamide

A solution of (S)-N-[2-(5-bromo-6-methoxyindan-1-yl) ethyl]propionamide (56.7 g, 174 mmol.) in dichloromethane (400 mL) was cooled to −30° C. To the solution was added dropwise slowly boron tribromide (95.8 g, 382 mmol.). The reaction mixture was stirred for 30 minutes while keeping at temperatures ranging from −20 to −15° C. The reaction mixture was poured into ice-water, which was stirred for further 10 minutes at room temperature. The organic matter was extracted with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 51.12 g, 94%).

$[\alpha]_D^{20}$=+2.7° (c 1.001, ethanol) m.p.: 146–148° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.5 Hz), 1.50–1.80 (2H, m), 1.90–2.40 (1H, m), 2.20–2.40 (1H, m), 2.24 (2H, q, J=7.5 Hz), 2.65–2.95 (2H, m), 3.00–3.18 (1H, m), 3.38 (2H, q, J=7.1 Hz), 5.82 (1H, br s), 6.86 (1H, s), 7.27 (1H, s), hidden (1H); Elemental Analysis for $C_{14}H_{18}BrNO_2$: Calcd.: C 53.86; H 5.81; N 4.49; Found: C 53.85; H 5.78; N 4.52

Reference Example 32

(S)-N-[2-(6-allyloxy-5-bromoindan-1-yl)ethyl] propionamide

A solution of (S)-N-[2-(5-bromo-6-hydroxyindan-1-yl) ethyl]propionamide (48.8 g, 156 mmol.) in N,N-dimethylformamide (110 mL) was cooled with ice, to which was gradually added sodium hydride (6.35 g, 172 mmol., content 65%). The mixture was stirred for about 15 minutes. When the bubbling of hydrogen gas ceased, allyl bromide (22.7 g, 188 mmol.) was added, and the mixture was stirred for 30 minutes under ice-cooling. The reaction mixture was poured into ice-water, which was neutralized with dilute hydrochloric acid. The organic matter was extracted with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel gel column chromatography (ethyl acetate) to afford the title compound (yield 52.97 g, 96%).

$[\alpha]_D^{20}$=+3.7° (c 1.003, ethanol); m.p.: 86–87° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.5 Hz), 1.48–1.80 (2H, m), 1.90–2.40 (2H, m), 2.20 (2H, q, J=7.5 Hz), 2.70–2.91 (2H, m), 3.00–3.20 (1H, m), 3.37 (2H, q, J=7.4 Hz), 4.59 (2H, m), 5.25–5.60 (3H, m), 5.97–6.20 (1H, m), 6.76 (1H, s), 7.37 (1H, s); Elemental Analysis for $C_{17}H_{22}BrNO_2$: Calcd.: C 57.96; H 6.29; N 3.98; Found: C 57.91; H 6.28; N 4.04

Reference Example 33

(S)-N-[2-(7-allyl-5-bromo-6-hydroxyindan-1-yl)ethyl] propionamide

A suspension of (S)-N-[2-(6-allyloxy-5-bromoindan-1-yl) ethyl]propionamide (50.75 g, 144 mmol.) in N,N-diethylaniline (150 mL) was stirred for 2.5 hours at 200–205° C. under argon atmosphere. The reaction mixture was cooled, followed by distilling off N,N-diethylaniline under reduced pressure to leave an oily residue. To the residue were added water (50 mL), 2N HCl (50 mL) and ethyl acetate (100 mL). The mixture was subjected to extraction twice to extract the organic matter. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate:hexane=7:3) to afford the title compound (yield 40.6 g, 80%).

$[\alpha]_D^{20}$=−51.3° (c 1.003, ethanol); m.p.: 85–87° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 1.45–2.13 (4H, m), 2.18 (2H, q, J=7.6 Hz), 2.68–3.65 (7H, m), 4.93–5.13 (2H, m), 5.41 (1H, br s), 5.49 (1H, s), 5.89–6.10 (1H, m), 7.20 (1H, s); Elemental Analysis for $C_{17}H_{22}BrNO_2$: Calcd.: C 57.96; H 6.29; N 3.98; Br 22.68; Found: C 57.95; H 6.22; N 4.00; Br 22.52

Reference Example 34

(S)-N-[2-(5-bromo-6-hydroxy-7-(2-hydroxyethyl)indan-1-yl)ethyl]propionamide

A solution of (S)-N-[2-(7-allyl-5-bromo-6-hydroxyindan-1-yl)ethyl]propionamide (588 mg, 1.67 mmol.) in methanol (30 mL) was cooled to about −70° C., to which was introduced ozone for 5 minutes. After confirming the disappearance of the starting material, an excess amount of powdery sodium borohydride (510 mg, 13.4 mmol.) was added to reaction mixture at about −70° C. to decompose ozonide. The reaction mixture was warmed to room temperature, which was neutralized with dilute hydrochloric acid, followed by extracting the organic matter with a mixture of ethyl acetate:butanol=1:1. The extract solution was dried over anhydrous magnesium sulfate, from which the solvent was distilled off under reduced pressure. The residue was then washed with diethyl ether to afford the title compound (yield 0.59 g, 99%).

[α]D^{20}=−43.7° (c 1.002, ethanol) m.p.: 85–87° C. (recrystallized from ethyl acetate/methanol); NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7.5 Hz), 1.40–2.10 (4H, m), 2.17 (2H, q, J=7.5 Hz), 2.62–3.01 (4H, m), 3.07–3.22 (1H, m), 3.28 (2H, q, J=6.8 Hz), 3.89 (2H, br s), 5.47 (1H, t, J=3.7 Hz), 6.31 (1H, br s), 7.20 (1H, s), 9.07 (1H, s); Elemental Analysis for $C_{16}H_{22}BrNO_3$: Calcd.: C 53.94; H 6.22; N 3.93; Br 22.43; Found: C 53.97; H 6.09; N 3.97; Br 22.40

Reference Example 35

(S)-N-[2-(6-hydroxy-7-(2-hydroxyethyl)indan-1-yl) ethyl]propionamide

A methanol suspension of (S)-N-[2-(5-bromo-6-hydroxy-7-(2-hydroxyethyl)indan-1-yl)ethyl]propionamide (590 mg, 1.66 mmol.), triethylamine (184 mg, 1.82 mmol.) and 5% palladium-carbon (100 mg) was subjected to catalytic reduction under hydrogen atmosphere. At the time when the calculated volume of hydrogen was absorbed, the catalyst was filtered off. The filtrate was made weakly acidic with dilute hydrochloric acid, followed by extracting the organic matter with a mixture of ethyl acetate:butanol=1:1. The extract solution was dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure, followed by washing with diethyl ether to afford the title compound (yield 0.42 g, 91%).

$[\alpha]_D^{20}$=−69.7 (c 1.002, ethanol); m.p.: 144–146° C. (recrystallized from ethyl acetate/methanol); NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.7 Hz), 1.45–2.10 (4H, m), 2.16 (2H, q, J=7.7 Hz), 2.60–3.00 (4H, m), 3.10–3.23 (1H, m), 3.29 (2H, q, J=6.8 Hz), 3.86 (2H, q, J=5.5 Hz), 5.00 (1H, t, J=4.4 Hz), 6.41 (1H, br s), 6.69 (1H, d, J=7.9 Hz), 6.91 (1H, d, J=7.9 Hz), 8.86 (1H, s); Elemental Analysis for $C_{16}H_{23}NO_3$: Calcd.: C 69.29; H 8.36; N 5.05; Found: C 69.46; H 8.28; N 5.11

Reference Example 36

6,7-Dimethoxy-1-indanone

In substantially the same manner as in Reference Example 18, the title compound was produced from 4-bromo-6,7-dimethoxy-1-indanone (yield 84%) as an oily product.

NMR ($CDCl_3$) δ: 2.69 (2H, t, J=6.0 Hz), 3.04 (2H, t, J=6.0 Hz), 3.89 (3H, s), 4.00 (3H, s), 7.10 (1H, d, J=8.4 Hz), 7.19 (1H, d, J=8.4 Hz)

Reference Example 37

(E)-(6,7-dimethoxyindan-1-ylidene)acetonitrile

In substantially the same manner as in Reference Example 7, the title compound was produced from 6,7-dimethoxy-1-indanone and diethyl cyanomethyl phosphonate (yield 81%).

m.p.: 111–113° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 2.95–3.15 (4H, m), 3.87 (3H, s), 3.91 (3H, s), 6.24 (1H, t, J=2.4 Hz), 6.95 (1H, d, J=8.6 Hz), 7.00 (1H, d, J=8.6 Hz); Elemental Analysis for $C_{13}H_{13}NO_2$: Calcd.: C 72.54; H 6.09; N 6.51; Found: C 72.38; H 6.11; N 6.53

Reference Example 38

2-(6,7-dimethoxyindan-1-yl)ethylamine hydrochloride

To a suspension of (E)-(6,7-dimethoxyindan-1-ylidene) acetonitrile (1.8 g, 8.36 mmol.) in ethanol (10 mL) were added Raney nickel (2.5 g, W2) and 4M ammonium/ethanol solution (20 mL). The mixture was stirred for 6 hours at 60° C. under hydrogen atmosphere (4 to 5 atm.). The reaction mixture was subjected to filtration, and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in ethanol (50 mL), to which was added 5% Pd-C (0.2 g, 50% hydrous). The mixture was stirred for 4 hours at room temperature under hydrogen atmosphere (normal pressure). The reaction mixture was subjected to filtration, and the filtrate was concentrated to leave (E)-2-(6,7-dimethoxyindan-1-yl)ethylamine. The compound was dissolved in ethanol (2 mL), to which was added a saturated hydrogen chloride/ethanol solution. The resulting crystalline precipitate was collected by filtration to afford the title compound (yield 1.68 g, 78%).

m.p.: 141–143° C. (recrystallized from ethanol); NMR (d_6-DMSO) δ: 1.59–1.83 (2H, m), 1.95–2.26 (2H, m), 2.60–2.94 (4H, m), 3.21–3.41 (1H, m), 3.75 (3H, s), 3.76 (3H, s), 6.83 (1H, d, J=8.4 Hz), 6.89 (1H, d, J=8.4 Hz), 7.99 (2H, br s); Elemental Analysis for $C_{18}H_{19}NO_2$.HCl: Calcd.: C 60.58; H 7.82; N 5.43; Cl 13.75; Found: C 60.03; H 7.55; N 5.66; Cl 14.11

Reference Example 39

N-[2-(6,7-dimethoxyindan-1-yl)ethyl]acetamide

In substantially the same manner as in Reference Example 12, the tile compound was produced from 2-(6,7-dimethoxyindan-1-yl)ethylamine and acetyl chloride (yield 83%).

m.p.: 79–81° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.70–1.93 (3H, m), 1.95 (3H, s), 2.15–2.36 (1H, m), 2.67–3.21 (3H, m), 3.25–3.53 (2H, m), 3.85 (3H, s), 3.87 (3H, s), 5.90 (1H, br s), 6.75 (1H, d, J=8.1 Hz), 6.91 (1H, d, J=8.1 Hz); Elemental Analysis for $C_{15}H_{21}NO_3$: Calcd.: C 68.42; H 8.94; N 5.32; Found: C 68.16; H 7.78; N 5.35

Reference Example 40

N-[2-(6,7-dimethoxyindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 12, the title compound was produced from 2-(6,7-dimethoxyindan-1-yl)ethylamine and propionyl chloride (yield 86%).

m.p.: 90–92° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.7 Hz), 1.70–1.94 (3H, m), 2.10–2.36 (1H, m), 2.18 (2H, q, J=7.7 Hz), 2.65–3.20 (3H, m), 3.25–3.55 (2H, m), 3.85 (3H, s), 3.87 (3H, s), 5.90 (1H, br s), 6.75 (1H, d, J=8.0 Hz), 6.90 (1H, d, J=8.0 Hz); Elemental Analysis for $C_{16}H_{23}NO_3$: Calcd.: C 69.29; H 8.36; N 5.05; Found: C 69.23; H 8.09; N 5.14

Reference Example 41

N-[2-(6,7-dimethoxyindan-1-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 12, the title compound was produced from 2-(6,7-dimethoxyindan-1-yl)ethylamine and butyryl chloride (yield 84%).

m.p.: 66–68° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.57–1.95 (5H, m), 2.10–2.35 (1H, m), 2.13 (2H, t, J=7.3 Hz), 2.66–3.20 (3H, m), 3.26–3.55 (2H, m), 3.85 (3H, s), 3.87 (3H, s), 5.87 (1H, br s), 6.75 (1H, d, J=8.1 Hz), 6.90 (1H, d, J=8.1 Hz); Elemental Analysis for $C_{17}H_{25}NO_3$: Calcd.: C 70.07; H 8.65; N 4.81; Found: C 69.84; H 8.43; N 4.80

Reference Example 42

N-[2-(6,7-dihydroxyindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 31, the title compound was produced from N-[2-(6,7-dimethoxyindan-1-yl)ethyl]propionamide (yield 73%).

m.p.: 98–101° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.5 Hz), 1.60–1.98 (3H, m), 2.10–2.30 (1H, m), 2.31 (2H, q, J=7.5 Hz), 2.60–3.15 (3H, m), 3.22–3.40 (1H, m), 3.52–3.75 (1H, m), 5.95 (1H, s), 6.01 (1H, br s), 6.63 (1H, d, J=7.9 Hz), 6.74 (1H, d, J=7.9 Hz), 9.62 (1H, s); Elemental Analysis for $C_{14}H_{19}NO_3$: Calcd.: C 67.45; H 7.68; N 5.62; Found: C 67.35; H 7.60; N 5.66

Reference Example 43

N-[2-(6,7-dihydroxyindan-1-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 31, the title compound was produced from N-[2-6,7-dimethoxyindan-1-yl)ethyl]butyramide (yield 92%) as an oily product.

NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.5 Hz), 1.60–2.00 (5H, m), 2.10–2.30 (1H, m), 2.23 (2H, t, J=7.5 Hz), 2.60–2.78 (1H, m), 2.80–3.00 (1H, m), 3.03–3.21 (1H, m), 3.22–3.40 (1H, m), 3.42–3.61 (1H, m), 6.20 (1H, br s), 6.38 (1H, br s), 6.62 (1H, d, J=7.7 Hz), 6.74 (1H, d, J=7.7 Hz), 9.13 (1H, br s)

Reference Example 44

6-methoxy-7-nitro-1-indanone

To a solution of 6-methoxy-1-indanone (30.0 g, 185 mmol.) in conc. sulfuric acid (130 mL) was added a solution of potassium nitrate (24.3 g, 0.24 mol.) in conc. sulfuric acid (100 mL), while maintaining the inner temperature below 0° C. The mixture was stirred for 20 minutes at the same temperature, which was then poured into ice-water, followed by extraction with ethyl acetate. The extract solution was washed with water and an aqueous solution of sodium hydrogencarbonate, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to afford the title compound (yield 21.7 g, 58%).

m.p.: 155–158° C.; NMR ($CDCl_3$) δ: 2.78 (2H, t, J=5.6 Hz), 3.13 (2H, t, J=5.6 Hz), 3.94 (3H, s), 7.34 (1H, d, J=8.4 Hz), 7.56 (1H, d, J=8.4 Hz)

Reference Example 45

(E)-(6-methoxy-7-nitroindan-1-ylidene)acetonitrile

In substantially the same manner as in Reference Example 7, the title compound was produced from 6-methoxy-7-nitro-1-indanone and diethyl cyanomethylphosphonate (yield 84%).

m.p.: 138–141° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 3.00–3.20 (4H, m), 3.92 (3H, s), 5.42 (1H, t, J=2.6 Hz), 7.14 (1H, d, J=8.6 Hz), 7.43 (1H, d, J=8.6 Hz)

Reference Example 46

(E)-(7-amino-6-methoxyindan-1-ylidene)acetonitrile

In substantially the same manner as in Reference Example 3, the title compound was produced from (E)-(6-methoxy-7-nitroindan-1-ylidene)acetonitrile (yield 79%).

m.p.: 119–121° C. (recrystallized from hexane/ethyl acetate); NMR ($CDCl_3$) δ: 2.90–3.20 (4H, m), 3.87 (3H, s), 4.23 (2H, br s), 5.60 (1H, t, J=2.2 Hz), 6.69 (1H, d, J=8.0 Hz), 6.84 (1H, d, J=8.0 Hz)

Reference Example 47

N-[2-(7-amino-6-methoxyindan-1-yl)ethyl]acetamide

In substantially the same manner as in Reference Example 38, 2-(7-amino-6-methoxyindan-1-yl)ethylamine was produced from (E)-(7-amino-6-methoxyindan-1-ylidene) acetonitrile. The crude product thus obtained was used, without further purification, for the reaction described below. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.3 g, 17.2 mmol.) and 1-hydroxybenzotriazole monohydrate (2.2 g, 14.4 mmol.) were suspended in N,N-dimethylformamide (30 mL). To the suspension was added, under ice-cooling, acetic acid (0.65 mL). This reaction mixture was stirred for one hour at room temperature, which was again cooled with ice. To the mixture was added dropwise a solution of the above-mentioned crude 2-(7-amino-6-methoxyindan-1-yl) ethylamine in N,N-dimethylformamide (10 mL). The mixture was stirred for 30 minutes, which was poured into water. The mixture was subjected to extraction with ethyl acetate. From the organic layer was extracted the hydrochloride with 2N hydrochloric acid. Then, the aqueous layer thus obtained was adjusted to pH 10 with a 4N aqueous solution of sodium hydroxide. From the aqueous layer, the organic matter was extracted with ethyl acetate, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate:ethanol=10:1) to afford the title compound (yield 1.6 g, 66%).

m.p.: 94–97° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.60–2.10 (6H, m), 2.20 (1H, m), 2.74 (1H, m), 2.92 (1H, m), 3.18 (1H, m), 3.32 (2H, q, J=5.0 Hz), 3.78 (2H, br s), 3.83 (3H, s), 5.70 (1H, br s), 6.59 (1H, d, J=8.0 Hz), 6.60 (1H, d, J=8.0Hz)

Reference Example 48

N-[2-(7-amino-6-methoxyindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 47, the title compound was produced from (E)-(7 -amino-6-methoxyindan-1-ylidene)acetonitrile and propionic acid (yield 40%).

m.p.: 71–73° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7.5 Hz), 1.6–2.0 (3H, m), 2.12 (2H, q, J=7.5 Hz), 2.25 (1H, m), 2.7–3.2 (3H, m), 3.34 (2H, q, J=5.0 Hz), 3.80 (2H, br s), 3.83 (3H, s), 5.67 (1H, br s), 6.59 (1H, d, J=8.0 Hz), 6.66 (1H, d, J=8.0 Hz)

Reference Example 49

N-[2-(7-amino-6-methoxyindan-1-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 47, the title compound was produced from (E)-(7-amino-6-methoxyindan-1-ylidene)acetonitrile and butyric acid (yield 71%).

m.p.: 65–68° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz), 1.50–2.40 (8H, m), 2.60–3.20 (3H, m), 3.34 (2H, q, J=5.1 Hz), 3.80 (2H, br s), 3.83 (3H, s), 5.67 (1H, br s), 6.59 (1H, d, J=8.2 Hz), 6.66 (1H, d, J=8.2 Hz)

Reference Example 50

N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl]acetamide hydrochloride

To a solution of N-[2-(7-amino-6-methoxyindan-1-yl) ethyl]acetamide (1.1 g, 4.4 mmol.) in dichloromethane (20 mL) was added dropwise gradually boron tribromide (2.1 mL, 22.1 mmol.). The mixture was stirred for 30 minutes at the same temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with 10% methanol/chloroform. The extract solution was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (chloroform:methanol=10:1) to afford N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl]acetamide (yield 630 mg, 61%). A portion of the product was dissolved in ethanol, to which was added a saturated hydrochloric acid/ethanol solution. The solvent was distilled off under reduced pressure. The resulting crystalline precipitate was recrystallized from ethanol to afford the title compound.

m.p.: 225–228° C. (recrystallized from ethanol); NMR (d_6-DMSO) δ: 1.30–1.80 (2H, m), 1.83 (3H, s), 1.90–2.20 (2H, m), 2.60–3.50 (5H, m), 6.79 (1H, d, J=8.2 Hz), 6.99 (1H, d, J=8.2 Hz), 7.96 (1H, br s), 10.32 (1H, br s), hidden (2H)

Reference Example 51

N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 50, the title compound was produced from N-[2-(7-amino-6-methoxyindan-1-yl)ethyl]propionamide (yield 88%) as an oily product.

NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7.5 Hz), 1.60–2.00 (3H, m), 2.14 (2H, q, J=7.5 Hz), 2.23 (1H, m), 2.70–2.90 (2H, m), 3.19 (1H, m), 3.34 (2H, q, J=5.1 Hz), 4.10 (2H, br s), 5.69 (1H, br s), 6.52 (1H, d, J=7.6 Hz), 6.60 (1H, d, J=7.6 Hz), hidden (1H)

Reference Example 52

N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 50, the title compound was produced from N-[2-(7-amino-6-methoxyindan-1-yl)ethyl]butyramide (yield 89%) as an oily product.

NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz), 1.50–1.90 (6H, m), 2.04 (2H, t, J=7.2 Hz), 2.23 (1H, m), 2.60–2.90 (2H, m), 3.10–3.40 (3H, m), 4.40 (2H, br s), 5.86 (1H, br s), 6.50 (1H, d, J=8.0 Hz), 6.62 (1H, d, J=8.0 Hz)

Reference Example 53

N-[2-(5-bromo-6-(2-propynyl)oxyindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 32, the title compound was produced from N-[2-(5-bromo-6-hydroxyindan-1-yl)ethyl]propionamide and propargyl bromide (yield 99%).

m.p.: 104–107° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.6 Hz), 1.50–2.40 (6H, m), 2.55 (1H, t, J=2.3 Hz), 2.7–3.2 (3H, m), 3.38 (2H, t, J=7.6 Hz), 4.76 (2H, d, J=2.3 Hz), 5.48 (1H, br s), 6.93 (1H, s), 7.38 (1H, s)

Reference Example 54

N-[2-(6-allyloxy-5-bromoindan-1-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 32, the title compound was produced from N-[2-(5-bromo-6-hydroxyindan-1-yl)ethyl]propionamide and allyl bromide (yield 93%).

NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.5 Hz), 1.60–2.20 (4H, m), 2.32 (2H, q, J=7.5 Hz), 2.6–3.2 (3H, m), 3.32 (2H, q, J=5.3 Hz), 4.60 (2H, d, J=4.6 Hz), 5.28 (1H, d, J=10.6 Hz), 5.43 (1H, s), 5.52 (1H, br s), 6.05 (1H, m), 6.78 (1H, s), 7.35 (1H, s)

Reference Example 55

N-[2-(5-bromo-6-(2-methyl-2-propenyl)oxyindan-1-yl) ethyl]propionamide

In substantially the same manner as in Reference Example 32, the title compound was produced from N-[2-(5-bromo-6-hydroxyindan-1-yl)ethyl]propionamide and methallyl chloride (yield 84%).

m.p.: 105–108° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.16 (3H, t,J=7.6 Hz), 1.86 (3H, s), 1.9–2.4 (6H, m), 2.80 (2H, m), 3.08 (1H, m), 3.38 (2H, q, J=7.6 Hz), 4.47 (2H, s), 5.00 (1H, s), 5.17 (1H, s), 5.40 (1H, br s), 6.76 (1H, s), 7.37 (1H, s)

Reference Example 56

N-[2-(7-allyl-5-bromo-6-hydroxyindan-1-yl)ethyl] propionamide

In substantially the same manner as in Reference Example 33, the title compound was produced from N-[2-(5-bromo-6-allyloxyindan-1-yl)ethyl]propionamide (yield 87%) as an oily product.

NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 1.50–2.10 (4H, m), 2.18 (2H, q, J=7.6 Hz), 2.70–3.70 (7H, m), 4.90–5.20 (2H, m), 5.41 (1H, br s), 5.49 (1H, s), 5.90–6.20 (1H, m), 7.20 (1H, s)

Reference Example 57

N-[2-(5-bromo-6-hydroxy-7-(2-methyl-2-propenyl) indan-1-yl) ethyl]propionamide

In substantially the same manner as in Reference Example 33, the title compound was produced from N-[2-(5-bromo-6-(2-methyl-2-propenyl)oxyindan-1-yl)ethyl]propionamide (yield 91%).

m.p.: 89–91° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 1.40–1.80 (2H, m), 1.80 (3H, s), 1.90–2.10 (2H, m), 2.17 (2H, q, J=7.6 Hz), 2.60–3.50 (7H, m), 4.49 (1H, s), 4.79 (1H, s), 5.32 (1H, br s), 5.47 (1H, s), 7.21 (1H, s)

Reference Example 58

(R)-N-[2-(6-methoxyindan-1-yl)ethyl]acetamide

A solution prepared by adding degasified absolute methanol (70 mL) to (E)-N-[2-(6-methoxyindan-1-ylidene) ethyl] acetamide (119.0 mg, 0.515 mmol.) and $Ru(OCOCH_3)_2$ [(R)-BINAP] (40 mg, 50 μmol.) was transferred to an autoclave, which was stirred for 6 hours at 50° C. under hydrogen pressure of 100 atm. The reaction mixture was subjected to high performance liquid chromatography using a chiral column to find that the asymmetric yield of (R)-N-[2-(6-methoxyindan-1-yl)ethyl]acetamide was 81%ee and the chemical yield was 82%.

Reference Example 59

(S)-N-[2-(6-ethoxyindan-1-yl)ethyl)propionamide

A solution prepared by adding degasified absolute methanol (70 mL) to (E)-N-[2-(6-ethoxyindan-1-ylidene) ethyl] propionamide (239.5 mg, 0.924 mmol.) and $Ru(OCOCH_3)_2$ [(S)-BINAP] (78 mg, 93 μmol.) was transferred to an autoclave, which was stirred for 6 hours at 50° C. under vapor pressure of 100 atm. The reaction mixture was subjected to analysis by means of high performance chromatography using a chiral column to find that the asymmetric yield of (S)-N-[2-(6-ethoxyindan-1-yl)ethyl]propionamide was 95%e.e. and the chemical yield was 88%.

Reference Example 60

(R)-N-[2-(6-methoxyindan-1-yl)ethyl]propionamide

A solution prepared by adding degasified absolute methanol (70 mL) to (Z)-N-[2-(6-methoxyindan-1-ylidene) ethyl] propionamide (258.5 mg, 1.05 mmol.) and $Ru(OCOCH_3)_2$ [(S)-BINAP] (84 mg, 100 μmol.) was transferred to an autoclave, which was stirred for 3 hours at 70° C. under hydrogen pressure of 100 atm. The reaction mixture was subjected to analysis by means of high performance liquid chromatography using a chiral column to find that the asymmetric yield of (R)-N-[2-(6-methoxyindan-1-yl)ethyl] propionamide was 80%e.e. and the chemical yield was 95%.

Reference Example 61

(R)-N-(2-(6-methoxyindan-1-yl)ethyl]propionamide

A solution prepared by adding 70 ml of degasified absolute methanol to (Z)-N-[2-(6-methoxyindan-1-ylidene) ethyl]propionamide (245,5 mg, 1.0 mmol.) and Ru_2Cl_4[(S)-BINAP]$_2$$NEt_3$ (169 mg, 100 μmol.) was transferred to an autoclave, which was stirred for 6 hours at 70° C. under hydrogen pressure of 100 atm. The reaction mixture was subjected to analysis by means of high performance liquid chromatography using a chiral column to find that the asymmetric yield of (R)-N-[2-(6-methoxyindan-1-yl)ethyl] propionamide was 86%e.e. and the chemical yield was 82%.

Reference Example 62

6-Hydroxy-7-nitro-indanone

In substantially the same manner as in Reference Example 45, the title compound was produced from 6-hydroxy-1-indanone (yield 61%).

m.p.: 218–220° C. (recrystallized from ethanol/hexane); NMR ($CDCl_3$) δ: 2.37 (2H, t, J=5.5 Hz), 2.74 (2H, t, J=5.5 Hz), 2.95 (1H, s), 6.95 (1H, d, J=8.4 Hz), 7.15 (1H, d, J=8.4 Hz)

Reference Example 63

Ethyl [(4-nitro-3-oxoindan-5-yl)oxy]acetate

To a solution of 6-hydroxy-7-nitro-1-indanone (8.0 g, 41 mmol.) in N,N-dimethylformamide (50 mL) was added potassium carbonate (11.7 g, 82 mmol.). The mixture was stirred under ice-cooling, to which was added dropwise ethyl bromoacetate (5.5 mL, 50 mmol.). The reaction mixture was then stirred for one hour at room temperature, which was poured into ice-water, followed by extracting the organic matter with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The resulting crystalline precipitate was collected by filtration and washed with hexane to afford the title compound (yield 10.8 g, 94%).

m.p.: 137–139° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz), 2.79 (2H, t, J=6.0 Hz), 3.14 (2H, t, J=6.0 Hz), 4.25 (2H, q, J=7.1 Hz), 4.74 (2H, s), 7.25 (1H, d, J=8.4 Hz), 7.55 (1H, d, J=8.4 Hz)

Reference Example 64

Ethyl [(4-amino-3-oxoindan-5-yl)oxy]acetate

In substantially the same manner as in Reference Example 3, the title compound was produced from ethyl [(4-nitro-3-oxoindan-5-yl)oxy]acetate (yield 98%).

NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz), 2.3–3.0 (4H, m), 4.28 (2H, q, J=7.1 Hz), 4.61 (2H, s), 5.89 (2H, br s), 6.53 (1H, d, J=8.2 Hz), 6.87 (1H, d, J=8.2 Hz)

Reference Example 65

7,8-Dihydroindeno[5,4-b][1,4]oxazine-2,9(1H,3H)-dione

To a solution of ethyl [(4-amino-3-oxoindan-5-yl) oxy] acetate (8.7 g, 34.9 mmol.) in toluene (200 mL) was added potassium t-butoxide (400 mg, 3.6 mmol.). The mixture was refluxed for 12 hours under argon atmosphere. The reaction mixture was cooled, which was poured into water, followed by neutralization with dilute hydrochloric acid. The organic matter was extracted with ethyl acetate, which was washed with a saturated aqueous saline solution and water, followed by drying over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (hexane:ethyl acetate=1:1) to afford the title compound (yield 4.8 g, 66%).

m.p.: 136–139° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 2.74 (2H, t, J=5.8 Hz), 3.10 (2H, t, J=5.8 Hz), 4.68 (2H, s), 7.01 (1H, d, J=7.2 Hz), 7.17 (1H, d, J=7.2 Hz), 9.52 (1H, br s)

Reference Example 66

(E)-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b][1,4]oxazin-9-ylidene)acetonitrile

In substantially the same manner as in Reference Example 7, the title compound was produced from 7,8-dihydroindeno[5,4-b][1,4]oxazine-2,9(1H,3H)-dione and diethyl cyanomethylphosphonate (yield 86%).

m.p.: 158–161° C. (recrystallized from chloroform); NMR ($CDCl_3$) δ: 3.00–3.20 (4H, m), 4.62 (2H, s), 5.62 (1H, t, J=2.3 Hz), 6.97 (1H, d, J=8.2 Hz), 7.06 (1H, d, J=8.2 Hz), 8.07 (1H, br s)

Reference Example 67

N-[2-(5-Hydroxyindol-3-yl)ethyl]propionamide

To a solution of serotonin hydrochloride (10 g, 47.5 mmol.) in water (50 mL) were added, under argon atmosphere, tetrahydrofuran (20 mL) and a solution of sodium carbonate (5.3 g) in water (20 mL). The mixture was cooled to 0° C., to which was added propionic anhydride (6.2 g, 49.9 mmol.). The mixture was stirred for 2 hours at room temperature. The reaction mixture was subjected to extraction with ethyl acetate. The extract solution was washed with 1N HCl, a saturated aqueous solution of sodium hydrogencarbonate and water, which was dried and then concentrated to afford the title compound (yield 10.0 g, 98.0%) as an oily product. This compound was used, without refining further, for the subsequent reaction.

NMR (d_6-DMSO) δ: 1.01 (3H, t, J=7.6 Hz), 2.09 (2H, q, J=7.6 Hz), 2.73 (2H, t, J=7.2 Hz), 3.30 (2H, q, J=7.2 Hz), 3.72 (1H, br s), 6.61 (1H, dd, J=8.8 & 2.2 Hz), 6.85 (1H, d, J=2.2 Hz), 7.04 (1H, s), 7.15 (1H, d, J=8.8 Hz), 7.91 (1H, t, J=7.2 Hz), 10.45 (1H, s)

Reference Example 68

N-[2-(5-allyloxyindol-3-yl)ethyl]propionamide

Allyl bromide (11 g, 90.8 mmol.) was added, under argon atmosphere, to a mixture of N-[2-(5-hydroxyindol-3-yl)ethyl]propionamide (20.0 g, 92.5 mmol.), cesium carbonate (31.6 g, 97 mmol.) and N,N-dimethylformamide (150 mL) at 0° C. The reaction mixture was stirred for one hour at 50° C., to which was added water. The product was extracted with ethyl acetate. The extract solution was washed with water and dried. The solvent was then distilled off to leave the title compound (yield 20.0 g, 79.4%) as an oily product. This product was used, without further purification, for the subsequent reaction.

NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7.6 Hz), 2.14 (2H, q, J=7.6 Hz), 2.92 (2H, t, J=7.0 Hz), 3.58 (2H, q, J=7.0 Hz), 4.57 (2H, dt, J=5.6 & 1.6 Hz), 5.28 (1H, dq, J=10.6 & 1.4 Hz), 5.35 (1H, dq, J=17.2 & 1.4 Hz), 5.61 (1H, t, J=7.0 Hz), 6.10 (1H, m), 6.89 (1H, dd, J=8.8 & 2.2 Hz), 6.99 (1H, d, J=2.2 Hz), 7.05 (1H, d, J=2.6 Hz), 7.25 (1H, d, J=8.8 Hz), 8.33 (1H, br s)

Reference Example 69

N-[2-(4-allyl-5-hydroxyindol-3-yl)ethyl]propionamide

In N,N-diethylaniline (100 mL) was dissolved N-[2-5-allyloxyindol-3-yl)ethyl]propionamide (20.0 g, 73.4 mmol.). The solution was heated for 6 hours at 200° C. under argon atmosphere. The reaction mixture was cooled. The solvent then separated was removed, and the residue was dissolved in ethyl acetate. This solution was washed with 1N HCl and a saturated aqueous solution of sodium hydrogencarbonate, followed by drying and concentration. The concentrate was purified by means of silica gel column chromatography (hexane: ethyl acetate=8:2) to give 14.1 g (yield 71%) of the title compound.

NMR (d_6-DMSO) δ: 1.03 (3H, t, J=7.2 Hz), 2.11 (2H, q, J=7.2 Hz), 2.91 (2H, t, J=7.4 Hz), 3.31 (2H, q, J=7.4 Hz), 3.67 (2H, d, J=5.2 Hz), 4.86 (1H, d, J=9.2 Hz), 4.90 (1H, d, J=8.0 Hz), 6.00 (1H, m), 6.68 (1H, d, J=8.4 Hz), 7.02 (1H, d, J=8.4 Hz), 7.87 (1H, t, J=5.0 Hz), 8.35 (1H, s), 10.49 (1H, s), hidden (1H)

Reference Example 70

N-[2-(4-allyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]propionamide

To a solution of N-[2-(4-allyl-5-hydroxyindol-3-yl)ethyl]propionamide (3.73 g, 14.3 mmol) in acetic acid (20 mL) was added sodium cyanoborohydride (2.7 g, 43.0 mmol) portionwise maintaining the reaction temperature around 15° C. The mixture was stirred for 1 hour maintaining the temperature 15 to 20° C. and then poured into water. The product was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, brine and water, dried over anhydrous magnesium sulfate and evaporated to afford the title compound. This compound was used for the subsequent reaction without further purification.

Reference Example 71

N-[2-(4-allyl-1-formyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]propionamide

Formic acid (3.3 g, 71.7 mmol) and acetic anhydride (7.32g, 71.7 mmol) was mixed under ice-cooling and the

mixture was stirred for 10 minutes. To the mixture was added a solution of N-[2-(4-allyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]propionamide in formic acid (10 mL). The mixture was stirred for 1 hour under ice-cooling and poured into water. The product was extracted with 10% methanol/ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, brine and water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=9:1) to afford the title compound (yield 2.0 g, 46% from N-[2-(4-allyl-5-hydroxyindol-3-yl)ethyl]propionamide).

m.p.: 173–175 ° C. (recrystallized from methanol/ethyl acetate); NMR (d_6-DMSO) δ: 1.01 (3H, dt, J=1.6 & 7.6 Hz), 1.30–1.50 (1H, m), 1.60–1.87 (1H, m), 2.08 (2H, dq, J=1.6 & 7.6 Hz), 3.00–3.50 (5H, m), 3.60–4.10 (2H, m), 4.90–5.10 (2H, m), 5.80–6.04 (1H, m), 6.65 (1H, d, J=8.4 Hz), 7.08, 7.59 (1H, d×2, J=8.4 Hz), 7.86 (1H, br s), 8.36, 8.85 (1H, s×2), 9.17, 9.23 (1H, s×2); Elemental Analysis for $C_{17}H_{22}N_2O_3$: Calcd.: C 67.53; H 7.33; N 9.26; Found: C 67.25; H 7.26; N 9.25

Reference Example 72

N-[2-[1-formyl-2,3-dihydro-5-hydroxy-4-(2-hydroxyethyl)indol-3-yl]ethyl]propionamide

In substantially the same manner as in Reference Example 34, the title compound was produced from N-[2-(4-allyl-1-formyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]propionamide as an oily product (yield 66%).

NMR (d_6-DMSO) δ: 1.00 (3H, dt, J=2.2 & 7.4 Hz), 1.30–1.55 (1H, m), 1.58–2.02 (1H, m), 2.06 (2H, dq, J=2.2 & 7.4 Hz), 2.50–2.80 (2H, m), 2.95–3.20 (2H, m), 3.22–4.00 (5H, m), 4.70–4.80 (1H, m), 6.62 (1H, d, J=8.4 Hz), 7.05, 7.57 (1H, d×2, J=8.4 Hz), 7.81 (1H, br s), 8.36, 8.84 (1H, s×2), 9.16, 9.21 (1H, s×2)

Reference Example 73

N-[2-(5-hydroxyindol-3-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 67, the title compound was produced from serotonin hydrochloride and butyryl chloride as an oily product (yield 39%)

NMR (d_6-DMSO) δ: 0.86 (3H, t, J=7.4 Hz), 1.49 (2H, sextet, J=7.4 Hz), 2.05 (2H, q, J=7.4 Hz), 2.72 (2H, t, J=7.4 Hz), 3.29 (2H, q, J=6.8 Hz), 6.59 (1H, dd, J=8.4 & 1.8 Hz), 6.83 (1H, d, J=1.8 Hz), 7.03 (1H, s), 7.12 (1H, d, J=8.4 Hz), 7.87 (1H, t, J=7.4 Hz), 8.59 (1H, s), 10.47 (1H, s)

Reference Example 74

N-[2-(5-allyloxyindol-3-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 68, the title compound was produced from N-[2-(5-hydroxyindol-3-yl)ethyl]butyramide and allyl bromide as an oily product (yield 91%).

NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.4 Hz), 1.62 (2H, sextet, J=7.4 Hz), 2.09 (2H, t, J=7.4 Hz), 2.92 (2H, t, J=7.0 Hz), 3.61 (2H, q, J=7.0 Hz), 4.57 (2H, d, J=5.6 Hz), 5.27 (1H, dq, J=10.2 & 1.4 Hz), 5.43 (1H, dq, J=17.2 & 1.4 Hz), 5.63 (1H, t, J=7.0 Hz), 5.80–6.20 (1H, m), 6.89 (1H, dd, J=8.8 & 2.2 Hz), 6.98 (1H, d, J=1.8 Hz), 7.05 (1H, d, J=2.2 Hz), 7.25 (1H, d, J=8.8 Hz), 8.37 (1H, br s)

Reference Example 75

N-[2-(4-allyl-5-hydroxyindol-3-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 69, the title compound was produced from N-[2-(5-allyloxyindol-3-yl)ethyl]butyramide as an oily product (yield 90%).

NMR (d_6-DMSO) δ: 0.88 (3H, t, J=7.4 Hz), 1.54 (2H, sextet, J=7.4 Hz), 2.07 (2H, t, J=7.4 Hz), 2.90 (2H, t, J=7.4 Hz), 3.31 (2H, q, J=7.4 Hz), 3.67 (2H, d, J=5.2 Hz), 4.86 (1H, dd, J=9.2 & 1.8 Hz), 4.93 (1H, d, J=1.4 Hz), 5.80–6.20 (1H, m), 6.68 (1H, d, J=8.4 Hz), 6.99 (1H, s), 7.02 (1H, d, J=8.4 Hz), 7.90 (1H, t, J=5.0 Hz), 8.36 (1H, s), 10.49 (1H, s)

Reference Example 76

N-[2-(4-allyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 70, the title compound was produced from N-[2-(4-allyl-5-hydroxyindol-3-yl)ethyl]butyramide as an oily product (yield 84%).

NMR (d_6-DMSO) δ: 0.86 (3H, t, J=7.3 Hz), 1.40–1.80 (4H, m), 2.06 (2H, t, J=7.3 Hz), 3.00–3.70 (8H, m), 4.91–5.07 (2H, m), 5.80–6.01 (1H, m), 6.63 (1H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 7.88 (1H, t, J=5.5 Hz), 9.13 (1H, s)

Reference Example 77

N-[2-(4-allyl-1-formyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]butyramide

In substantially the same manner as in Reference Example 71, the title compound was produced from N-[2-(4-allyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]butyramide as an oily product (yield 75%).

NMR (d_6-DMSO) δ: 0.86 (3H, t, J=7.3 Hz), 1.25–1.83 (4H, m), 2.04 (2H, t, J=7.3 Hz), 3.00–3.40 (5H, m), 3.60–4.03 (2H, m), 4.90–5.10 (2H, m), 5.80–6.01 (1H, m), 6.64 (1H, d, J=8.4 Hz), 7.08, 7.59 (1H, d×2, J=8.4 Hz), 7.88 (1H, br s), 8.36, 8.85 (1H, s×2), 9.17, 9.22 (1H, s×2); Elemental Analysis for $C_{18}H_{24}N_2O_3$: Calcd.: C 68.33; H 7.65; N 8.85; Found: C 68.17; H 7.65; N 8.99

Reference Example 78

N-[2-[1-formyl-2,3-dihydro-5-hydroxy-4-(2-hydroxyethyl)indol-3-yl]ethyl]butyramide

In substantially the same manner as in Reference Example 34, the title compound was produced from N-[2-(4-allyl-1-formyl-2,3-dihydro-5-hydroxyindol-3-yl)ethyl]butyramide as an oily product (yield 69%).

NMR (d_6-DMSO) δ: 0.85 (3H, t, J=7.3 Hz), 1.38–1.81 (4H, m), 2.03 (2H, t, J=7.3 Hz), 2.50–2.82 (2H, m), 2.98–4.00 (7H, m), 4.74–4.83 (1H, m), 6.62 (1H, d, J=8.1 Hz), 7.06, 7.57 (1H, d×2, J=8.1 Hz), 7.83 (1H, br s), 8.35, 8.83 (1H, s×2), 9.17, 9.22 (1H, s×2)

Reference Example 79

(2,3-dihydrobenzofuran-5-yl)methanol

To a solution of 2,3-dihydrobenzofuran-5-carbaldehyde (30.0 g, 0.202 mol) in methanol (150 mL) was added sodium borohydride (3.83 g, 0.101 mol) under ice-cooling. The mixture was stirred for 15 minutes at ambient temperature and then diluted with water. The product was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to afford the title compound (yield 27.6 g, 91%) as an oily product.

NMR ($CDCl_3$) δ: 1.67 (1H, s), 3.20 (2H, t, J 8.6 Hz), 4.57 (2H, t, J=8.6 Hz), 4.58 (2H, s), 6.76 (1H, d, J=8.0 Hz), 7.10 (1H, d, J=8.0 Hz), 7.22 (1H, s)

Reference Example 80

5-bromomethyl-2,3-dihydrobenzofuran

To a solution of (2,3-dihydrobenzofuran-5-yl)methanol (29.0 g, 0.193 mol) in tetrahydrofuran (150 mL) was added phosphorous tribromide (34.8 g, 0.129 mol) under ice/salt-cooling. The mixture was stirred for 20 minutes and then poured into water. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford the title compound (yield 27.6 g, 91%).

m.p.: 57-60° C.; NMR ($CDCl_3$) δ: 3.20 (2H, t, J=8.8 Hz), 4.51 (2H, s), 4.59 (2H, t, J=8.8 Hz), 6.73 (1H, d, J=8.2 Hz), 7.14 (1H, d, J=8.2 Hz), 7.24 (1H, s)

Reference Example 81

Ethyl 3-(2,3-dihydrobenzofuran-5-yl)-2-phenylpropionate

To a solution of lithium hexamethyldisilazide solution, prepared from 1,1,1,3,3,3-hexamethyldisilazane (37.4 g, 0.232 mol), n-butyllithium (127 mL, 1.6 M hexane solution) and tetrahydrofuran (150 mL), was added a solution of ethyl phenylacetate (33.3 g, 0.203 mol) in tetrahydrofuran (20 mL) at −78° C. The mixture was stirred for 15 minutes and then a solution of 5-bromomethyl-2,3-dihydrobenzofuran (41.0 g, 0.193 mol) in tetrahydrofuran (50 mL) was added. The mixture was stirred for further 20 minutes, diluted with water and warmed up to room temperature. The product was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) to afford the title compound as an oily product (yield 54.5 g, 95%).

NMR ($CDCl_3$) δ: 1.13 (3H, t, J=6.8 Hz), 2.93 (1H, dd, J=6.2 & 13.8 Hz), 3.14 (2H, t, J=8.8 Hz), 3.32 (1H, dd, J=9.0 & 13.8 Hz), 3.78 (1H, dd, J=6.2 & 9.0 Hz), 4.00–4.15 (2H, m), 4.52 (2H, t, J=8.8 Hz), 6.64 (1H, d, J=8.2 Hz), 6.87 (1H, d, J=8.2 Hz), 6.96 (1H, s), 7.21–7.38 (5H, m)

Reference Example 82

Ethyl 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionate

In substantially the same manner as in Reference Example 4, the title compound was produced from 3-(2,3-dihydrobenzofuran-5-yl)-2-phenylpropionic acid as an oily product (yield 97%).

NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.2 Hz), 2.89 (1H, dd, J=6.2 & 13.8 Hz), 3.23 (2H, t, J=8.6 Hz), 3.29 (1H, dd, J=8.8 & 13.8 Hz), 3.75 (1H, dd, J=6.2 & 8.8 Hz), 4.12 (2H, q, J=7.2 Hz), 4.62 (2H, t, J=8.6 Hz), 6.87 (1H, s), 7.04 (1H, s), 7.30–7.32 (5H, m)

Reference Example 83

Ethyl 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionate

In substantially the same manner as in Reference Example 15, the title compound was produced from ethyl 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionate as an oily product (yield 35%).

NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.0 Hz), 3.11 (1H, dd, J=5.4 & 14.0 Hz), 3.19 (2H, t, J=8.8 Hz), 3.50 (1H, dd, J=9.4 & 14.0 Hz), 3.96 (1H, dd, J=5.4 & 9.4 Hz), 4.08 (2H, q, J=7.0 Hz), 4.64 (2H, t, J=8.8 Hz), 6.92 (1H, s), 7.28–7.32 (5H, m)

Reference Example 84

3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionic acid

In substantially the same manner as in Reference Example 5, the title compound was produced from ethyl 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionate (yield 56%).

m.p.: 188–189° C. (ethyl acetate/hexane); NMR ($CDCl_3$) δ: 3.06–3.21 (3H, m), 3.50 (1H, dd, J=8.8 & 14.0 Hz), 4.01 (1H, dd, J=5.8 Hz, 8.8 Hz), 4.63 (2H, t, J=8.8 Hz), 6.85 (1H, s), 7.32 (5H, s), hidden (1H)

Reference Example 85

4,5-dibromo-1,2,6,7-tetrahydro-7-phenyl-8H-indeno[5,4-b]furan-8-one

In substantially the same manner as in Reference Example 6, the title compound was produced from 3-(6,7-dibromo-2,3-dihydrobenzofuran-5-yl)-2-phenylpropionic acid (yield 81%).

m.p.: 208–211° C.; NMR ($CDCl_3$) δ: 3.19 (1H, dd, J=3.9 & 17.7 Hz), 3.55 (2H, t, J=9.0 Hz), 3.61 (1H, dd, J=8.3 & 17.7 Hz), 3.92 (1H, dd, J=3.9 & 8.3 Hz), 4.81 (2H, t, J=9.0 Hz), 7.15–7.45 (5H, m)

Reference Example 86

1,2,6,7-tetrahydro-7-phenyl-8H-indeno[5,4-b]furan-8-one

In substantially the same manner as in Reference Example 18, the title compound was produced from 4,5-dibromo-1,2,6,7-tetrahydro-7-phenyl-8H-indeno[5,4-b]furan-8-one (yield 70%).

m.p.: 108–110° C.; NMR ($CDCl_3$) δ: 3.12 (1H, dd, J=4.0 & 16.8 Hz), 3.38 (2H, t, J=8.8 Hz), 3.53 (1H, dd, J=8.1& 16.8 Hz), 3.79 (1H, dd, J=4.0 & 8.1 Hz), 4.57 (2H, t, J=8.8 Hz), 6.98 (1H, d, J=8.4 Hz), 7.07–7.29 (6H, m)

Reference Example 87

(E)-(1,6,7,8-tetrahydro-7-phenyl-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile, and

(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)acetonitrile

To a boiling solution of 1,2,6,7-tetrahydro-7-phenyl-8H-indeno[5,4-b]furan-8-one (4.4 g, 17.6 mmol) in tetrahydrofuran (100 mL) was added the phosphonate ylide solution, prepared from diethyl cyanomethylphosphonate (3.27 g, 18.5 mmol), sodium hydride (60% oil dispersion, 0.73 g, 18.5 mmol) and tetrahydrofuran (80 mL). The mixture was refluxed for 1.5 hours. To this solution was added the same amount of the phosphonate ylide solution additionally. The mixture was refluxed for further 30 minutes, cooled and then poured into water. The product was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1), followed by crystallization from ethyl acetate/diisopropylether to afford the mixture of (A) (E)-(1,6,7,8-tetrahydro-7-phenyl-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile and (B) (1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)acetonitrile (A:B=1:2) (yield 0.85 g, 18%).

m.p.: 123–126° C.; NMR ($CDCl_3$) δ: (A) 3.03 (1H, dd, J=17.2 & 1.8 Hz), 3.32 (2H, dt, J=11.4 & 2.2 Hz), 3.59 (1H, dd, J=17.2 & 8.4 Hz), 4.48 (1H, dt, J=8.4 & 1.8 Hz), 4.68 (2H, t, J=11.4 Hz), 5.53 (1H, d, J=1.8 Hz), 6.91 (1H, d, J=8.0 Hz), 7.10–7.60 (6H, m) (B) 3.61 (2H, t, J=8.8 Hz), 3.68 (2H,

s), 3.75 (2H, s), 4.68 (2H, t, J=8.8 Hz), 6.73 (1H, d , J=8.0 Hz), 7.10–7.60 (6H, m)

Example 1

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethyl]acetamide

Aqueous 1 N sodium hydroxide solution (1.5 ml) and acetic anhydride (0.050 ml, 0.528 mmols) were added to a tetrahydrofuran (1.5 ml) solution of 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrobromide (0.10 g, 0.352 mmols), and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from isopropyl ether/hexane to obtain 0.057g (yield: 66%) of the target compound.

m.p.: 78–79° C.; NMR ($CDCl_3$) δ: 1.53–2.12 (3H, m), 1.96 (3H, s),2.20–2.38 (1H, m),2.70–2.96 (2H, m),3.02–3.40 (5H, m), 4.45–4.68 (2H, m), 5.46 (1H, br s), 6.62 (1H, d, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz); Elemental Analysis for $C_{15}H_{19}NO_2$: Calcd.: C 73.44; H 7.81; N 5.71; Found: C 73.55; H 7.90; N 5.60

Example 2

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethyl]propionamide

In the same manner as in Example 1, the target compound was obtained from 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b] furan-8-yl)ethylamine hydrobromide and propionyl chloride. The yield was 78%.

m.p.: 102–104° C. (recrystallized from isopropyl ether/ hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 1.55–2.38 (4H, m), 2.18 (2H, q, J=7.6 Hz), 2.69–2.99 (2H, m), 3.02–3.40 (5H, m), 4.42–4.63 (2H, m), 5.61 (1H, br s), 6.62 (1H, d, J=7.8 Hz), 6.95 (1H, d, J=7.8 Hz); Elemental Analysis for $C_{16}H_{21}NO_2$: Calcd.: C 74.10; H 8.16; N 5.40; Found: C 74.20; H 8.37; N 5.25

Example 3

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl] acetamide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and acetic anhydride. The yield was 54%.

m.p.: 185–186° C. (recrystallized from methanol/ isopropyl ether); NMR ($CDCl_3$) δ: 1.96 (3H, s), 2.03–2.15 (2H, m), 3.09 (2H, t, J=6.8 Hz), 3.20 (2H, t, J=6.8 Hz), 3.56 (2H, q, J=6.4 Hz), 4.18 (2H, t, J=7.0 Hz), 5.60 (1H, br s), 6.73 (1H, d, J=8.8 Hz), 6.96 (1H, d, J=2.2 Hz), 7.09 (1H, d, J=8.8 Hz), 7.98 (1H, br s); Elemental Analysis for $C_{15}H_{18}N_2O_2$: Calcd.: C 69.74; H 7.02; N 10.84; Found: C 69.69; H 7.09; N 10.79

Example 4

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl] propionamide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and propionyl chloride. The yield was 67%.

m.p.: 147–148° C. (recrystallized from methanol/ isopropyl ether); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 2.02–2.16 (2H, m), 2.17 (2H, q, J=7.6 Hz), 3.08 (2H, t, J=7.0 Hz), 3.19 (2H, t, J=7.0 Hz), 3.57 (2H, q, J=6.2 Hz), 4.18 (2H, t, J=5.0 Hz), 5.60 (1H, br s), 6.72 (1H, d, J=8.4 Hz), 6.94 (1H, d, J=2.2 Hz), 7.09 (1H, d, J=8.4 Hz), 8.11 (1H, br s); Elemental Analysis for $C_{16}H_{20}N_2O_2$: Calcd.: C 70.56; H 7.40; N 10.29; Found: C 70.69; H 7.54; N 10.27

Example 5

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl] butyramide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and butyryl chloride. The yield was 62%.

m.p.: 154–155° C. (recrystallized from methanol/ isopropyl ether); NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.57–1.73 (2H, m), 2.06–2.16 (4H, m), 3.08 (2H, t, J=6.8 Hz), 3.19 (2H, t, J=6.4 Hz), 3.52–3.63 (2H, m), 4.18 (2H, t, J=5.2 Hz), 5.58 (1H, br s), 6.72 (1H, d, J=8.4 Hz), 6.94 (1H, d, J=2.6 Hz), 7.09 (1H, d, J=8.4 Hz), 8.05 (1H, br s); Elemental Analysis for $C_{17}H_{22}N_2O_2$: Calcd.: C 71.30; H 7.74; N 9.78; Found: C 71.45; H 7.86; N 9.78

Example 6

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl) ethyl]acetamide

Platinum oxide (45 mg) and hydrochloric acid (2 ml) were added to an ethanol (40 ml) solution of N-[2-3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]acetamide (0.90 g, 3.48 mmols), and the mixture was stirred in a hydrogen atmosphere (at from 4 to 5 atmospheres) at 50° C. for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was neutralized with a saturated, aqueous sodium hydrogencarbonate solution, then saturated with salt and extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/isopropyl ether to obtain 0.53 g (yield: 59%) of the target compound.

m.p.: 137–138° C.; NMR ($CDCl_3$) δ: 1.78–2.05 (4H, m), 1.90 (3H, s), 2.68 (2H, t, J=6.6 Hz), 2.96–3.14 (1H, m), 3.31–3.50 (3H, m), 3.65 (1H, t, J=9.4 Hz), 3.98–4.10 (1H, m), 4.15–4.26 (1H, m), 6.13 (1H, br s), 6.49 (1H, d, J=8.4 Hz), 6.57 (1H, d, J=8.4 Hz), hidden (1H); Elemental Analysis for $C_{15}H_{20}N_2O_2$: Calcd.: C 69.20; H 7.74; N 10.76; Found: C 69.65; H 7.74; N 10.61

Example 7

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl) ethyl]propionamide

In the same manner as in Example 6, the target compound was obtained from N-[2-(3,7,8,9-tetrahydropyrano[3,2-e] indol-1-yl)ethyl]propionamide. The yield was 42%.

m.p.: 106–107° C. (recrystallized from ethyl acetate/ isopropyl ether); NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7.6 Hz), 1.76–2.08 (4H, m), 2.13 (2H, q, J=7.6 Hz), 2.68 (2H, t, J=6.4 Hz), 2.99–3.16 (1H, m), 3.31–3.51 (3H, m), 3.65 (1H, t, J=9.4 Hz), 3.98–4.10 (1H, m), 4.15–4.24 (1H, m), 6.10 (1H, br s), 6.48 (1H, d, J=8.4 Hz), 6.56 (1H, d, J=8.4 Hz), hidden (1H); Elemental Analysis for $C_{16}H_{22}N_2O_2$: Calcd.: C 70.04; H 8.08; N 10.21; Found: C 70.18; H 8.34; N 10.13

Example 8

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl) ethyl]butyramide

In the same manner as in Example 6, the target compound was obtained from N-[2-(3,7,8,9-tetrahydropyrano[3,2-e] indol-1-yl)ethyl]butyramide. The yield was 55%.

m.p.: 91–93° C. (recrystallized from ethyl acetate/ isopropyl ether); NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.2 Hz), 1.53–1.71 (2H, m), 1.76–1.88 (2H, m), 1.91–2.10 (2H, m), 2.05 (2H, q, J=8.2 Hz), 2.68 (2H, t, J=6.6 Hz), 2.99–3.16 (1H, m), 3.30–3.50 (3H, m), 3.64 (1H, t, J=9.2 Hz), 3.98–4.09 (1H, m), 4.15–4.23 (1H, m), 6.11 (1H, br s), 6.48 (1H, d, J=8.4 Hz), 6.56 (1H, d, J=8.4 Hz), hidden (1H); Elemental Analysis for $C_{17}H_{24}N_2O_2$: Calcd.: C 70.80; H 8.39; N 9.71; Found: C 70.55; H 8.45; N 9.68

Example 9

N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]-benzopyran-9-yl)ethyl]propionamide

A bromobenzene (15 ml) solution of N-[2-(5-fluoro-6-(2-propionyloxy)indan-1-yl)ethyl]propionamide (0.55 g, 1.90 mmols) was stirred at 250° C. in a sealed tube for 8 hours. The reaction mixture was cooled, and then the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate) to obtain 0.27 g (yield: 49%) of the target compound.

m.p.: 108–110° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.5 Hz), 1.50–1.81 (2H, m), 1.89–2.30 (2H, m), 2.18 (2H, q, J=7.5 Hz), 2.55–3.00 (2H, m), 3.16–3.40 (3H, m), 4.66–4.92 (2H, m), 5.40 (1H, br s), 5.88 (1H, dt, J=9.9 Hz, 3.7 Hz), 6.43–6.53 (1H, m), 6.80 (1H, d, J=10.6 Hz)

Example 10

N-[2-(5-fluoro-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide

In the same manner as in Reference Example 3, the target compound was obtained from N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide. The yield was 80%.

m.p.: 106–108° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.7 Hz), 1.47–1.84 (2H, m), 1.84–2.27 (4H, m), 2.17 (2H, q, J=7.7 Hz), 2.60–3.01 (4H, m), 3.05–3.20 (1H, m), 3.21–3.41 (2H, m), 4.05–4.20 (1H, m), 4.27–4.39 (1H, m), 5.40 (1H, br s), 6.77 (1H, d, J=10.6 Hz)

Example 11

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]-furen-8-yl)ethyl]propionamide

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide was optically resolved by high performance column chromatography [apparatus: LC Module 1 (Nippon Millipore Ltd.); column: Ceramospher RU-1 (10 (i.d.)×250 mm, Shiseido); mobile phase: methanol; flow rate: 4.4 ml/min; column temperature:50° C.; sample concentration: 17% (w/v); amount injected: 8.5 mg) to give the target compound.

$[\alpha]_D^{20}$=−57.8° (c 1.004, chloroform); m.p.: 11.3–115° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.7 Hz), 1.52–2.40 (4H, m), 2.17 (2H, q, J=7.7 Hz), 2.69–3.00 (2H, m), 3.01–3.40 (5H, m), 4.42–4.64 (2H, m), 5.40 (1H, br s), 6.62 (1H, d, J=7.7 Hz), 6.95 (1H, d, J=7.7 Hz); Elemental Analysis for $C_{16}H_{21}NO_2$: Calcd.: C 74.10; H 8.16; N 5.40; Found: C 73.86; H 7.97; N 5.47

Example 12

(R)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]-furan-8-yl)ethyl]propionamide

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide was optically resolved by high performance column chromatography in the same manner as in Example 11 to give the target compound.

$[\alpha]_D^{20}$=+57.80 (c 1.005, chloroform); m.p.: 113–115° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.7 Hz), 1.52–2.40 (4H, m), 2.17 (2H, q, J=7.7 Hz), 2.69–3.00 (2H, m), 3.01–3.40 (5H, m), 4.42–4.64 (2H, m), 5.40 (1H, br s), 6.62 (1H, d, J=7.7 Hz), 6.95 (1H, d, J=7.7 Hz); Elemental Analysis for $C_{16}H_{21}NO_2$: Calcd.: C 74.10; H 8.16; N 5.40; Found: C 73.97; H 7.97; N 5.47

Example 13

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide

In the same manner as in Example 1, the target compound was obtained from 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride and butyryl chloride. The yield was 67%.

m.p.: 55–57° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.51–1.90 (4H, m), 1.92–2.08 (1H, m), 2.12 (2H, t, J=7.3 Hz), 2.17–2.38 (1H, m), 2.68–2.98 (2H, m), 3.00–3.40 (5H, m), 4.41–4.68 (2H, m), 5.43 (1H, br s), 6.62 (1H, d, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz); Elemental Analysis for $C_{17}H_{23}NO_2$: Calcd.: C 74.69; H 8.48; N 5.12; Found: C 74.59; H 8.33; N 5.36

Example 14

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide

Acetyl chloride (0.24 g, 3.03 mmol) was slowly added dropwise to an ice-cooled solution of 2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydro-chloride (0.6 g, 2.52 mmol) and triethylamine (0.64 g, 6.31 mmol) in N,N-dimethylformamide (60 mL). After overnight stirring at room temperature, the reaction mixture was concentrated and poured into water, and the organic matter was extracted with ethyl acetate. The extract was washed with a satruated aqueous sodium chloride solution and water and then dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography (ethyl acetate:methanol=98:2) and further recrystallized from ethyl acetate to give 425 mg (yield: 70%) of the target compound.

m.p.: 153–155° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.98 (3H, s), 2.80 (2H, m), 3.31 (2H, br s), 3.43 (2H, t, J=8.6 Hz), 3.57 (2H, q, J=7.0 Hz), 4.60 (2H, d, J=8.6 Hz), 5.62 (1H, br s), 6.30 (1H, s), 6.67 (1H, d, J=7.9 Hz), 7.18 (1H, d, J=7.9 Hz); Elemental Analysis for $C_{15}H_{17}NO_2$: Calcd.: C 74.05; H 7.04; N 5.76; Found: C 73.98; H 7.06; N 5.92

Example 15

N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)-ethyl]propionamide

In the same manner as in Example 14, the target compound was obtained from 2-(1,6-dihydro-2H-indeno-[5,4-b]furan-8-yl)ethylamine hydrochloride and propionyl chloride. The yield was 90%.

m.p.: 131–133° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.7 Hz), 2.20 (2H, q, J=7.7 Hz), 2.80 (2H, m), 3.31 (2H, br s), 3.44 (2H, t, J=8.6 Hz), 3.58 (2H, q, J=7.0 Hz), 4.60 (2H, d, J=8.6 Hz), 5.60 (1H, br s), 6.29 (1H, s), 6.68 (1H, d, J=7.9 Hz), 7.19 (1H, d, J=7.9 Hz); Elemental Analysis for $C_{16}H_{19}NO_2$: Calcd.: C 74.68; H 7.44; N 5.44; Found: C 74.59; H 7.34; N 5.71

Example 16

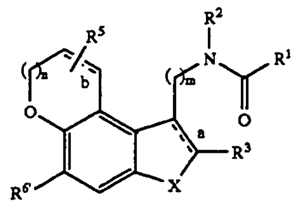
N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)-ethyl]butyramide

In the same manner as in Example 14, the target compound was obtained from 2-(1,6-dihydro-2H-indeno-[5,4-b]furan-8-yl)ethylamine hydrochloride and butyryl chloride. The yield was 95%.

m.p.: 131–133° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.58–1.76 (2H, m), 2.14 (2H, q, J=7.5 Hz), 2.80 (2H, m), 3.31 (2H, br s), 3.44 (2H, t, J=8.6 Hz), 3.58 (2H, q, J=6.8 Hz), 4.60 (2H, d, J=8.6 Hz), 5.60 (1H, br s), 6.29 (1H, s), 6.67 (1H, d, J=7.9 Hz), 7.18 (1H, d, J=7.9 Hz); Elemental Analysis for $C_{17}H_{21}NO_2$: Calcd.: C 75.25; H 7.80; N 5.16; Found: C 75.25; H 7.73; N 5.23

The chemical structures of the compounds obtained in Examples 1 to 16 are shown in Table 1 below.

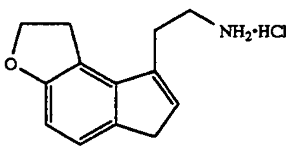
TABLE 1



Example No.	R^1	R^2	R^3	R^5	R^6	X	m	n	a	b	Optical rotation
1	Me	H	H	H	H	CH_2	2	0	-	-	
2	Et	H	H	H	H	CH_2	2	0	-	-	
3	Me	H	H	H	H	NH	2	1	=	-	
4	Et	H	H	H	H	NH	2	1	=	-	
5	Pr	H	H	H	H	NH	2	1	=	-	
6	Me	H	H	H	H	NH	2	1	-	-	
7	Et	H	H	H	H	NH	2	1	-	-	
8	Pr	H	H	H	H	NH	2	1	-	-	
9	Et	H	H	H	F	CH_2	2	1	-	=	
10	Et	H	H	H	F	CH_2	2	1	-	-	
11	Et	H	H	H	H	CH_2	2	0	-	-	-
12	Et	H	H	H	H	CH_2	2	0	-	-	+
13	Pr	H	H	H	H	CH_2	2	0	-	-	
14	Me	H	H	H	H	CH_2	2	0	=	-	
15	Et	H	H	H	H	CH_2	2	0	=	-	
16	Pr	H	H	H	H	CH_2	2	0	=	-	

Example 17

2-(1,6-Dihydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride

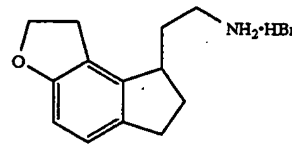


A saturated ammonia/ethanol solution (150 ml) and Raney cobalt (8.4 g) were added to an ethanol (150 ml) solution of (E)-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]-furan-8-ylidene)acetonitrile (2.6 g, 13.2 mmol), and the reaction mixture was stirred at room temperature in a hydrogen atmosphere (5 kgf/cm^2) for 3 hours. The Raney cobalt was filtered off and the solvent was distilled off under reduced pressure to give 2-(1,6,7,8-tetrahydro-2H-indeno(5,4-b]furan-8-ylidene)-ethylamine. To this residue was added a saturated hydrogen chloride/ethanol solution (100 ml), followed by 1 hour of heating under reflux. The reaction solution was concentrated and the residue obtained was recrystallized from ethanol to give 2.75 g (yield: 88%) of the target compound.

m.p.: 243–245° C. (recrystallized from ethanol); NMR (d_6-DMSO, D_2O) δ: 2.90 (2H, t, J=7.7 Hz), 3.13 (2H, t, J=7.7 Hz), 3.28 (2H, s) 3.40 (2H, t, J=8.7 Hz), 4.56 (2H, t, J=8.7 Hz), 6.41 (1H, s), 6.62 (1H, d, J=7.9 Hz), 7.19 (1H, d, J=7.9 Hz); Elemental Analysis for $C_{13}H_{15}NO.HCl$: Calcd.: C 65.68; H 6.78; N 5.89; Cl, 14.91; Found: C 65.81; H 6.83; N 5.90; Cl, 14.89

Example 18

2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine hydrobromide.



Raney nickel (0.4 g, W2) and 4 M ammonia/ethanol solution (10 ml) were added to an ethanol (30 ml) suspension of (E)-(4-bromo-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile (0.44 g, 1.59 mmols) and stirred in a hydrogen atmosphere (at from 4 to 5 atmospheres) at room temperature for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml), and 5% palladium-carbon (1 g, containing 50% water) was added thereto and stirred in a hydrogen atmosphere (at ordinary pressure) at room temperature for 4 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 0.42 g (yield: 93%) of the target compound. This was amorphous.

NMR ($CDCl_3$) δ: 1.58–1.83 (2H, m), 1.97–2.36 (2H, m), 2.70–2.96 (6H, m), 3.03–3.36 (3H, m), 4.42–4.64 (2H, m), 6.61 (1H, d, J=8.2 Hz), 6.95 (1H, d, J=8.2 Hz)

Example 19

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

Propionyl chloride (2.57 g, 27.8 mmol.) was gradually added dropwise, under ice-cooling, to a solution of (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl) ethylamine hydrochloride (5.55 g, 23.1 mmol.) and triethylamine (4.7 g, 46.3 mmol.) in N,N-dimethylformamide (100 ml). The mixture was stirred for one hour at room temperature, which was then poured into water, followed by extracting the organic matter with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate:methanol=98:2) to afford the title compound (yield 5.25 g, 88%).

m.p.: 113–115° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.7 Hz), 1.52–2.40 (4H, m), 2.17 (2H, q, J=7.7 Hz), 2.69–3.00 (2H, m), 3.01–3.40 (5H, m), 4.42–4.64 (2H, m), 5.40 (1H, br s), 6.62 (1H, d, J=7.7 Hz), 6.95 (1H, d, J=7.7 Hz); Elemental Analysis for $C_{16}H_{21}NO_2$: Calcd.: C 74.10; H 8.16; N 5.40; Found: C 73.83; H 8.12; N 5.23

Example 20

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

To a solution of (S)-N-[2-(6-hydroxy-7-(2-hydroxyethyl) indan-1-yl)ethyl]propionamide (5 g, 18 mmol.) in pyridine (14.6 mL), was added dropwise, while maintaining the temperature at about −10° C. under cooling with ice, methanesulfonyl chloride (1.4 mL, 18 mmol.). The reaction mixture was stirred for 25 minutes at temperatures ranging from −10 to −5° C. To the reaction mixture was further added dropwise methanesulfonyl chloride (0.7 mL, 9 mmol.). The mixture was stirred for further 25 minutes at temperatures ranging from −10 to −5° C. To the reaction mixture were added gradually ethyl acetate (10 mL) and a saturated aqueous solution of sodium hydrogencarbonate

(10 mL). The mixture was warmed to room temperature, followed by stirring for 30 minutes. The organic matter was extracted with ethyl acetate, which was washed with 2N HCl and water, followed by drying over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in ethyl acetate (20 mL). To the solution was added triethylamine (4.6 g, 45.1 mmol.), and the mixture was heated under reflux for 40 minutes. To the reaction mixture was added 2N HCl, which was subjected to extraction with ethyl acetate. The extract solution was washed with a saturated aqueous solution of sodium hydrogencarbonate and water, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent. The residue was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 4.04 g, 86%).

$[\alpha]_D^{20}$=−57.8° (c 1.004, chloroform); m.p.: 113–115° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.14 (3H, t, J 7.7 Hz), 1.52–2.40 (4H, m), 2.17 (2H, q, J=7.7 Hz), 2.69–3.00 (2H, m), 3.01–3.40 (5H, m), 4.42–4.64 (2H, m), 5.40 (1H, br s), 6.62 (1H, d, J=7.7 Hz), 6.95 (1H, d, J=7.7 Hz); Elemental Analysis for $C_{16}H_{21}NO_2$: Calcd.: C 74.10; H 8.16; N 5.40; Found: C 73.86; H 7.97; N 5.47

Example 21

N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl) ethyl]propionamide

Hexamethyl phosphoramide (5 mL) was cooled with ice, to which was gradually added sodium hydride (0.28 g, 7.5 mmol.), content 65%). To this mixture was added dropwise a solution of N-[2-(6,7-dihydroxyindan-1-yl)ethyl] propionamide (0.85 g, 3.41 mmol.) in hexamethyl phosphoramide (5 mL) at room temperature over 6 minutes. At the time when the bubbling of hydrogen gas ceased, diiodomethane (1.1 g, 4.1 mmol.) was added dropwise to the reaction mixture, followed by stirring for two hours at room temperature. The reaction mixture was poured into water, which was neutralized with dilute hydrochloric acid, followed by extracting the organic matter with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 280 mg, 31%).

m.p.: 102–104° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.7 Hz), 1.70–1.89 (2H, m), 1.90–2.10 (1H, m), 2.15–2.40 (1H, m), 2.20 (2H, q, J=7.7 Hz), 2.68–3.00 (2H, m), 3.13–3.36 (2H, m), 3.40–3.59 (1H, m), 3.68(1H, br s), 5.92 (2H, dd, J=1.5 & 9.9 Hz), 6.67 (2H, s); Elemental Analysis for $C_{15}H_{19}NO_3$: Calcd.: C 68.94; H 7.33; N 5.36; Found: C 68.89; H 7.28; N 5.42

Example 22

N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl) ethyl]butyramide

A solution of N-[2-(6,7-dihydroxyindan-1-yl)ethyl] butyramide (1.13 g, 4.29 mmol.), dibromomethane (2.98 g, 17.2 mmol.), potassium carbonate (1.78 g, 12.9 mmol.) and copper-(II) oxide (34 mg, 0.43 mmol.) in N,N-dimethylformamide (15 mL) was stirred for 3 hours at 110° C. The reaction mixture was cooled, which was poured into water, followed by neutralizing with dilute hydrochloric acid. The organic matter was extracted with ethyl acetate. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 785 mg, 67%).

m.p.: 71–73° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.57–2.40 (6H, m), 2.15 (2H, t, J=7.5 Hz), 2.67–3.00 (2H, m), 3.15–3.34 (2H, m), 3.39–3.58 (1H, m), 5.67 (1H, s), 5.91 (2H, dd, J=1.5 & 9.5 Hz), 6.67 (2H, s); Elemental Analysis for $C_{16}H_{21}NO_3$: Calcd.: C 69.79; H 7.69; N 5.09; Found: C 69.75; H 7.40; N 5.28

Example 23

N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-yl)ethyl]propionamide

In substantially the same manner as in Example 22, the title compound was produced from N-[2-(6,7-dihydroxyindan-1-yl)ethyl]propionamide and 1,2-dibromoethane (yield 80%).

m.p.: 120–122° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 1.60–2.00 (3H, m), 2.10–2.32 (1H, m), 2.19 (2H, q, J=7.5 Hz), 2.61–3.01 (2H, m), 3.08–3.53 (3H, m), 4.25 (4H, br s), 5.67 (1H, br s), 6.69 (2H, s); Elemental Analysis for $C_{16}H_{21}NO_3$: Calcd.: C 69.79; H 7.69; N 5.09; Found: C 69.90; H 7.61; N 5.20

Example 24

N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-yl)ethyl]butyramide

In substantially the same manner as in Example 22, the title compound was produced from N-[2-(6,7-dihydroxyindan-1-yl)ethyl]butyramide and 1,2-dibromoethane (yield 90%).

m.p.: 84–87° C. (recrystallized from ethyl acetate/diethyl ether/petroleum ether); NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.7 Hz), 1.57–2.00 (5H, m), 2.14 (2H, t, J=7.3 Hz), 2.18–2.34 (1H, m), 2.61–3.01 (2H, m), 3.10–3.55 (3H, m), 4.25 (4H, s), 5.65 (1H, br s), 6.60 (2H, s); Elemental Analysis for $C_{17}H_{23}NO_3$: Calcd.: C 70.56; H 8.01; N 4.84; Found: C 70.45; H 7.85; N 4.98

Example 25

N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl] acetamide

To a solution of N-[2-(7-amino-6-hydroxyindan-1-yl) ethyl]acetamide (630 mg, 2.7 mmol.) in methanol (5 mL) were added dropwise, under ice-cooling, methyl orthoformate (7.4 mL, 67.3 mmol.) and a saturated HCl/methanol (1.4 mL) solution. The reaction mixture was stirred for 30 minutes at room temperature and for further one hour at 60° C. The reaction mixture was cooled, which was poured into ice-water, followed by extracting the organic matter with chloroform. The extract solution was washed with a saturated aqueous saline solution and water, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent. The residue was purified by means of silica gel column chromatography (chloroform:methanol=20:1) to afford the title compound (yield 520 mg, 79%).

m.p.: 89–92° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.88–2.02 (3H, m), 2.04 (3H, s), 2.34–2.53 (1H, m), 2.86–3.19 (3H, m), 3.59–3.72 (2H, m), 6.94 (1H, br s), 7.25 (1H, d, J=8.4 Hz), 7.40 (1H, d, J=8.4 Hz), 8.09 (1H, s); Elemental Analysis for $C_{14}H_{16}N_2O_2$: Calcd.: C 68.83; H 6.60; N 11.47; Found: C 68.64; H 6.43; N 11.50

Example 26

N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl] propionamide

In substantially the same manner as in Example 25, the title compound was obtained from N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl]propionamide and methyl orthoformate (yield 79%).

m.p.: 81–84° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.5 Hz), 1.80–2.10 (3H, m), 2.27 (2H, q, J=7.5 Hz), 2.37–2.53 (1H, m), 2.80–3.20 (3H, m), 3.55–3.80 (2H, m), 6.93 (1H, br s), 7.25 (1H, d, J=8.8 Hz), 7.40 (1H, d, J=8.8 Hz), 8.09 (1H, s); Elemental Analysis for $Cl_5Hl_8N_2O_2$: Calcd.: C 69.75; H 7.02; N 10.84; Found: C 69.76; H 6.90; N 10.76

Example 27

N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl]butyramide

In substantially the same manner as in Example 25, the title compound was produced from N-[2-(7-amino-6-hydroxyindan-1-yl)ethyl)butyramide and methyl orthoformate (yield 90%).

m.p.: 65–68° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.4 Hz), 1.67–1.80 (2H, m), 1.80–2.12 (3H, m), 2.22 (2H, q, J=7.5 Hz), 2.33–2.53 (1H, m), 2.80–3.20 (3H, m), 3.50–3.73 (2H, m), 6.90 (1H, br s), 7.25 (1H, d, J=8.0 Hz), 7.40 (1H, d, J=8.0 Hz), 8.08 (1H, s); Elemental Analysis for $C_{16}H_{20}N_2O_2$: Calcd.: C 70.56; H 7.40; N 10.29; Found: C 70.48; H 7.30; N 10.45

Example 28

N-[2-(5-bromo-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide

A solution of N-[2-(5-bromo-6-(2-propynyl)oxyindan-1-yl)ethyl]propionamide (2.9 g, 8.4 mmol.) in bromobenzene (30 mL) was stirred for 18 hours in a sealed tube at 200° C. The reaction mixture was cooled and, then, the solvent was distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 2.5 g, 85%).

m.p.: 110–111° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.5 Hz), 1.50–2.50 (5H, m), 2.60–3.10 (3H, m), 3.15–3.25(1H, m), 3.32 (2H, q, J=7.5 Hz), 4.80–4.90 (2H, m), 5.40 (1H, br s), 5.88 (1H, dt, J=10.0 & 3.8 Hz), 6.45 (1H, dd, J=1.6 & 9.8 Hz), 7.18 (1H, s); Elemental Analysis for $C_{17}H_{20}BrNO_2$: Calcd.: C 58.30; H 5.76; N 4.00; Br 22.81; Found: C 58.17; H 5.54; N 3.98; Br 22.65

Example 29

N-[2-(5-bromo-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl)propionamide

To a solution of N-[2-(5-bromo-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide (1.2 g, 3.4 mmol.) in ethanol (10 mL) was added 5% Pd-C (120 mg, 50% hydrous). The mixture was stirred for one hour at room temperature under hydrogen atmosphere. The reaction mixture was subjected to filtration. The filtrate was concentrated under reduced pressure. The concentrate was purified by means of silica gel column chromatography (ethyl acetate) to afford the title compound (yield 327 mg, 27%).

m.p.: 114–116° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz), 1.50–2.30 (7H, m), 2.60–3.20 (6H, m), 3.30 (2H, q, J=7.6 Hz), 4.10–4.22 (1H, m), 4.30–4.42 (1H, m), 5.40 (1H, br s), 7.22 (1H, s); Elemental Analysis for $C_{17}H_{22}BrNO_2$: Calcd.: C 57.96; H 6.29; N 3.98; Br 22.68; Found: C 57.84; H 6.20; N 4.01; Br 22.42

Example 30

N-[2-(2,3,4,5,6,7-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide

To a solution of N-[2-(5-bromo-2,3,4,5,6,7-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide (200 mg, 0.6 mmol.) in ethanol (5 mL) was added 5% Pd-C (200 mg, 50% hydrous). The mixture was stirred for 3 hours at room temperature under hydrogen atmosphere. The reaction mixture was subjected to filtration. The filtrate was then concentrated under reduced pressure. The concentrate was purified by means of silica gel column chromatography to afford the title compound (yield 130 mg, 85%).

m.p.: 85–88° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.6 Hz), 1.80–2.10 (6H, m), 2.15 (2H, q, J=7.6 Hz), 2.60–3.50 (7H, m), 4.00–4.30 (2H, m), 5.35 (1H, br s), 6.63 (1H, d, J=8.2 Hz), 6.94 (1H, d, J=8.2 Hz); Elemental Analysis for $C_{17}H_{23}NO_2$: Calcd.: C 74.69; H 8.48; N 5.12; Found: C 74.56; H 8.25; N 5.16

Example 31

N-[2-(4-bromo-2,2-dimethyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

A solution of N-[2-(5-bromo-6-hydroxy-7-(2-methyl-2-propenyl)indan-1-yl)ethyl]propionamide (2.4 g, 6.5 mmol.) in methylene chloride (40 mL) was cooled with ice. To the solution was added dropwise gradually a diethyl ether boron trifluoride complex (4.0 mL, 32.5 mmol.). The reaction mixture was stirred for 3 hours under ice-cooling, which was poured into ice-water, followed by extracting the organic matter with ethyl acetate. The extract solution was washed with water and a saturated aqueous solution of sodium hydrogencarbonate, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was recrystallized from ethyl acetate/isopropyl ether to afford the title compound (yield 2.1 g, 89%).

m.p.: 98–101° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 1.48 (3H, s), 1.54 (3H, s), 1.76–2.02 (2H, m), 2.19 (2H, q, J=7.5 Hz), 2.25–2.38 (1H, m), 2.62–3.16 (6H, m), 3.32 (2H, q, J=5.3 Hz), 5.41 (1H, br s), 7.11 (1H, s); Elemental Analysis for $C_{18}H_{24}BrNO_2$: Calcd.: C 59.02; H 6.60; N 3.82; Br 21.81; Found: C 58.94; H 6.48; N 3.98; Br 21.97

Example 32

N-[2-(2,2-dimethyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b)furan-8-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 35, the title compound was produced from N-[2-(4-bromo-2,2-dimethyl-1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl]propionamide (yield 76%).

m.p.: 69–72° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.43 (3H, s), 1.50 (3H, s), 1.60–2.10 (2H, m), 2.13 (2H, q, J=7.5 Hz), 2.24–2.40 (1H, m), 2.60–3.20 (6H, s), 3.35 (2H, q, J=5.3 Hz), 5.39 (1H, br s), 6.55 (1H, d, J=7.6 Hz), 6.95 (1H, d, J=7.6 Hz); Elemental Analysis for $C_{18}H_{25}NO_2$: Calcd.: C 75.22; H 8.77; N 4.87; Found: C 74.98; H 8.74; N 4.96

Example 33

N-[2-(4-bromo-2-methyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

In substantially the same manner as in Example 31, the title compound was produced from N-[2-(5-bromo-6-hydroxy-7-allylindan-1-yl)ethyl]propionamide (yield 65%).

m.p.: 131–133° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.6 Hz), 1.46–2.40 (9H, m), 2.60–3.40 (7H, m), 4.90–5.03 (1H, m), 5.42 (1H, br s), 7.11 (1H, s); Elemental Analysis for $C_{17}H_{22}BrNO_2$: Calcd.: C 57.96; H 6.29; N 3.98; Br 22.68; Found: C 58.08; H 6.28; N 4.07; Br 22.80

Example 34

N-[2-(4-bromo-2-hydroxymethyl-2-methyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

A solution of N-[2-(5-bromo-6-hydroxy-7-(2-methyl-2-propenyl)indan-1-yl)ethyl]propionamide (550 mg, 1.5 mmol.) in dichloromethane (5 mL) was cooled with ice. To the solution were added triethylamine (0.2 mL, 1.5 mmol.) and methachloroperbenzoic acid (1.0 g, 4.1 mmol.). The mixture was stirred for two hours at room temperature. The reaction mixture was poured into an aqueous solution of sodium thiosulfate. The organic matter was extracted with

ethyl acetate. The extract solution was washed with 1N HCl and a saturated aqueous solution of sodium hydrogencarbonate, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent. The residue was dissolved in dichloromethane, to which was added triethylamine (1 mL). The mixture was stirred for 2 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by means of silica gel column chromatography (chloroform:methanol=10:1) to afford the title compound (yield 420 mg, 73%) as an oily product.

NMR ($CDCl_3$) δ: 1.00–1.20 (3H, m), 1.50–2.40 (10H, m), 2.60–3.81 (9H, m), 5.50 (1H, br s), 7.11 (1H, s); Elemental Analysis for $C_{18}H_{24}BrNO_3.0.5H_2O$: Calcd.: C 55.25; H 6.44; N 3.58; Br 20.42; Found: C 55.58; H 6.46; N 3.58; Br 20.28

Example 35

N-[2-(2-methyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

In substantially the same manner as in Reference Example 35, the title compound was produced from N-[2-(4-bromo-2-methyl-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide (yield 76%).

m.p.: 68–72° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.2 Hz), 1.43 (1.2H, d, J=6.2 Hz), 1.50 (1.8H, d, J=6.2 Hz), 1.60–2.40 (6H, m), 2.60–3.40 (7H, m), 4.80–5.00 (1H, m), 5.30–5.45 (1H, m), 6.58 (1H, d, J=8.0 Hz), 6.95 (1H, d, J=8.0 Hz); Elemental Analysis for $C_{17}H_{23}NO_2$: Calcd.: C 74.69; H 8.48; N 5.12; Found: C 74.62; H 8.55; N 5.24

Example 36

N-[2-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b][1,4]oxazin-9-yl)ethyl]propionamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (372.0 mg, 1.9 mmol.) and 1-hydroxybenzotriazole monohydrate (257 mg, 1.9 mmol.) were suspended in N,N-dimethylformamide (2.5 mL). To the suspension was added, under ice-cooling, propionic acid (0.11 mL, 1.4 mmol.). This reaction mixture was stirred for one hour at room temperature, and, then, cooled again with ice, to which was added dropwise a solution of 9-(2-aminoethyl)-1,7,8,9-tetrahydroindeno[5,4-b][1,4] oxazin-2(3H)-one (300 mg, 1.3 mmol.) in N,N-dimethylformamide (1.5 mL). The mixture was stirred for one hour under ice-cooling. The reaction mixture was poured into water, and the organic matter was extracted with ethyl acetate. The extract solution was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by means of silica gel column chromatography (chloroform:methanol=10:1) to afford the title compound (yield 253.0 mg, 88%).

m.p.: 216–219° C. (recrystallized from ethyl acetate/methanol); NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7.5 Hz), 1.50–2.00 (3H, m), 2.10–2.30 (3H, m), 2.70–3.10 (2H, m), 3.30–3.50 (3H, m), 4.59 (2H, s), 5.97 (1H, br s), 6.81 (2H, s), 9.77 (1H, br s);

Example 37

N-[2-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b](1,4)oxazin-9-yl)ethyl]butyramide

In substantially the same manner as in Example 36, the title compound was produced from 9-(2-aminoethyl)-1,7,8,9-tetrahydroindeno[5,4-b](1,4)oxazin-2(3)-one and butyric acid (yield 64%).

m.p.: 209–212° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.50–2.00 (5H, m), 2.10–2.30 (3H, m), 2.70–3.10 (2H, m), 3.20–3.50 (3H, m), 4.58 (2H, s), 5.93 (1H, br s), 6.80 (2H, s), 9.72 (1H, br s);

Example 38

N-[2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl) ethyl]propionamide

A solution of 9-(2-aminoethyl)-1,7,8,9-tetrahydro-indeno[5,4-b][1,4]oxazin-2(3H)-one (1.2 g, 5.3 mmol.) in tetrahydrofuran (30 mL) was was cooled with ice, to which was added lithium aluminum hydride (0.8 g, 21.4 mmol.). The mixture was heated for 18 hours under reflux under argon atmosphere. The reaction mixture was cooled, to which were added water (0.8 mL), a 15% aqueous solution of sodium hydroxide (0.8 mL) and water (2.4 mL), successively. The mixture was then stirred for 30 minutes at room temperature. Insolubles were filtered off, and the filtrate was concentrated under reduced pressure. Then, in substantially the same manner as in Example 36, from 2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl) ethylamine thus obtained and propionic acid, the title compound was produced (yield 250 mg, 51%).

m.p.: 80–83° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7.5 Hz), 1.50–2.30 (6H, m), 2.60–3.20 (3H, m), 3.32 (2H, q, J=6.7Hz), 3.43 (2H, t, J=4.4 Hz), 3.85 (1H, br s), 4.20 (2H, t, J=4.4 Hz), 5.84 (1H, br s), 6.50 (1H, d, J=8.0 Hz), 6.62 (1H, d, J=8.0 Hz);

Example 39

N-[2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl)ethyl]butyramide

In substantially the same manner as in Example 38, the title compound was produced from 9-(2-aminoethyl)-1,7,8,9-tetrahydroindeno[5,4-b][1,4]oxazin-2(3H)-one and butyric acid (yield 61%)

m.p.: 115–118° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.50–2.30 (8H, m), 2.60–3.20 (3H, m), 3.32 (2H, q, J=6.7 Hz), 3.45 (2H, t, J=4.4Hz), 3.80 (1H, br s), 4.22 (2H, t, J=4.4 Hz), 5.54 (1H, br s), 6.52 (1H, d, J=8.0 Hz), 6.63 (1H, d, J=8.0 Hz);

Example 40

N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide

To a solution of N-[2-[1-formyl-2,3-dihydro-5-hydroxy-4-(2-hydroxyethyl)indol-3-yl]ethyl]propionamide (0.8 g, 2.61 mmol) in pyridine (10 mL) was added methansulfonyl chloride (0.2 mL, 2.61 mmol.) around −10° C. The mixture was stirred for 20 minutes while keeping the temperature −10 to 5° C. To this was added additional methansulfonyl chloride (0.1 mL, 1.3 mmol.) and the mixture was stirred for further 15 minutes at the same temperature. The mixture was diluted with ethyl acetate(10 mL). Saturated aqueous sodium hydrogen carbonate solution (10 mL) was added slowly and the mixture was stirred for 30 minutes at room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 2N-hydrochloric acid and water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to afford the title compound (yield 0.25 g, 33%).

m.p.: 139–141° C. (recrystallized from ethyl acetate); NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.6 Hz), 1.62–2.11 (2H, m), 2.19 (2H, q, J=7.6 Hz), 3.01–3.50 (5H, m), 3.70–3.95 (1H, m), 4.07–4.30 (1H, m), 4.48–4.71 (2H, m), 5.70 (1H, br s), 6.63, 6.65 (1H,d×2, J=8.4 Hz), 6.92, 7.87 (1H, d×2, J=8.4 Hz), 8.43, 8.80 (1H, s×2); Elemental analysis for $C_{16}H_{20}N_2O_3$: Calcd.: C 66.65; H 6.99; N 9.72; Found: C 66.43; H 7.01; N 9.73

Example 41

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide

1) To a solution of N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide (0.18 g, 0.62 mmol.) in ethanol (5 mL) was added saturated hydrogen chloride/ethanol (15 mL). The mixture was stirred for 1.5 hours at 80° C. and then cooled. The solvent was removed in vacuo to afford the title compound as an amorphous product.

NMR (d_6-DMSO) δ: 1.01 (3H, t, J=7.5 Hz), 1.54–1.76 (1H, m), 1.88–2.10 (1H, m), 2.08 (2H, q, J=7.5 Hz),

3.00–3.95 (7H, m), 4.61 (2H, q, J=8.1 Hz), 6.76 (1H, d, J=8.4 Hz), 7.16 (1H, d, J=8.4 Hz), 7.98 (1H,br s), 11.23 (1H, br s), hidden (1H)

2) The hydrochloride was added to saturated aqueous sodium hydrogen carbonate solution and the resulting free base was extracted with 10% methanol/chloroform. The extract was washed with brine and water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (chloroform:methanol=9:1), followed by recrystallization to afford the title compound (yield 97 mg, 60%).

m.p.: 96–98° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.6 Hz), 1.70–2.06 (2H, m), 2.15 (2H, q, J=7.6 Hz), 2.99–3.50 (6H, m), 3.68 (1H, t, J=8.3 Hz), 4.40–4.63 (2H, m), 5.86 (1H, br s), 6.44 (1H, d, J=8.2 Hz), 6.52 (1H, d, J=8.2 Hz); Elemental analysis for $C_{15}H_{20}N_2O_2$: Calcd.: C 69.20; H 7.74; N 10.76; Found: C 68.80; H 7.48; N 10.73

Example 42

N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide

In substantially the same manner as in Example 40, the title compound was produced from N-[2-[1-formyl-2,3-dihydro-5-hydroxy-4-(2-hydroxyethyl)indol-3-yl-]ethyl] butyramide as an amorphous product (yield 55%)

NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.30–1.80 (4H, m), 2.17 (2H, t, J=7.3 Hz), 2.82–3.60 (5H, m), 3.80–4.26 (2H, m), 4.40–4.60 (2H, m), 5.77 (1H, br s), 6.61, 6.63 (1H, dx2, J=8.3 Hz), 6.92, 7.96 (1H, dx2, J=8.3 Hz), 8.40, 8.78 (1H, sx2)

Example 43

N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl] butyramide

In substantially the same manner as in Example 41, the title compound was produced from N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide as an amorphous amorphous product (yield 64%).

NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.50–1.90 (4H, m), 2.13 (2H, t, J=7.3 Hz), 3.00–3.50 (6H, m), 3.67 (1H, m), 4.40–4.60 (2H, m), 6.00 (1H, br s), 6.47 (1H, d, J=8.2 Hz), 6.55 (1H, d, J=8.2 Hz), hidden (1H)

Example 44

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl) ethyl]acetamide

In substantially the same manner as in Example 14, the title compound was produced from 2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride and acetyl chloride (yield 69%).

m.p.: 150–153° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.78 (3H, s), 2.96 (2H, t, J=7.2 Hz), 3.42 (2H, q, J=7.2 Hz), 3.53 (2H, t, J=8.6 Hz), 3.70 (2H, s), 4.63 (2H, t, J=8.6 Hz), 5.41 (1H, br s), 6.70 (1H, d, J=7.9 Hz), 7.21 (1H, d, J=7.9 Hz), 7.26–7.50 (5H, m)

Example 45

N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl) ethyl]propionamide

In substantially the same manner as in Example 1, the title compound was produced from 2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride and propionic anhydride (yield 67%).

m.p.: 166–168° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.7 Hz), 2.01 (2H, q, J=7.7 Hz), 2.96 (2H, t, J=7.3 Hz), 3.44 (2H, q, J=7.3 Hz), 3.54 (2H, t, J=8.6 Hz), 3.70 (2H, s), 4.63 (2H, t, J=8.6 Hz), 5.40 (1H, br s), 6.70 (1H, d, J=8.1 Hz), 7.21 (1H, d, J=8.1 Hz), 7.26–7.50 (5H, m)

Example 46

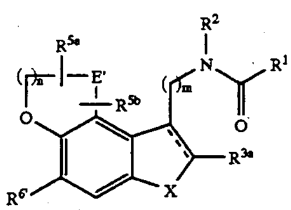
N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl) ethyl]butyramide

In substantially the same manner as in Example 14, the title compound was produced from 2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride and butyryl chloride (yield 71%).

m.p.: 172–175° C. (recrystallized from ethyl acetate/hexane); NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7.3 Hz), 1.40–1.62 (2H, m), 1.95 (2H, t, J=7.3 Hz), 2.96 (2H, t, J=7.1 Hz), 3.44 (2H, q, J=7.1 Hz), 3.54 (2H, t, J=8.8 Hz), 3.70 (2H, s), 4.63 (2H, t, J=8.8 Hz), 5.41 (1H, br s), 6.70 (1H, d, J=7.7 Hz), 7.21 (1H, d, J=7.7 Hz), 7.26–7.50 (5H, m)

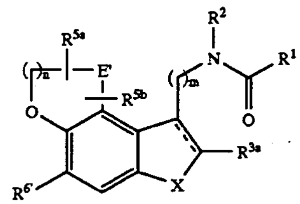
The chemical structures of the compounds obtained in Examples 19 to 46 are shown in Table 2 below.

TABLE 2



Example No.	R^1	R^2	R^{3a}	R^{5a}	R^{5b}	R^6	X	E'	m	n	☰	Optical rotation
19	Et	H	H	H	H	H	CH_2	CH_2CH_2	2	0	-	-
20	Et	H	H	H	H	H	CH_2	CH_2CH_2	2	0	-	-
21	Et	H	H	H	H	H	CH_2	CH_2O	2	0	-	
22	Pr	H	H	H	H	H	CH_2	CH_2O	2	0	-	
23	Et	H	H	H	H	H	CH_2	CH_2O	2	1	-	
24	Pr	H	H	H	H	H	CH_2	CH_2O	2	1	-	
25	Me	H	H	H	H	H	CH_2	CH=N	2	0	-	
26	Et	H	H	H	H	H	CH_2	CH=N	2	0	-	
27	Pr	H	H	H	H	H	CH_2	CH=N	2	0	-	
28	Et	H	H	H	H	Br	CH_2	CH=CH	2	1	-	
29	Et	H	H	H	H	Br	CH_2	CH_2CH_2	2	1	-	
30	Et	H	H	H	H	H	CH_2	CH_2CH_2	2	1	-	
31	Et	H	H	Me	Me	Br	CH_2	CH_2CH_2	2	0	-	
32	Et	H	H	Me	Me	H	CH_2	CH_2CH_2	2	0	-	

TABLE 2-continued

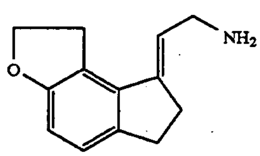


Example No.	R^1	R^2	R^{3a}	R^{5a}	R^{5b}	R^6	X	E'	m	n	≡	Optical rotation
33	Et	H	H	Me	H	Br	CH_2	CH_2CH_2	2	0	-	
34	Et	H	H	Me	CH_2OH	Br	CH_2	CH_2CH_2	2	0	-	
35	Et	H	H	Me	H	H	CH_2	CH_2CH_2	2	0	-	
36	Et	H	H	H	H	H	CH_2	CONH	2	1	-	
37	Pr	H	H	H	H	H	CH_2	CONH	2	1	-	
38	Et	H	H	H	H	H	CH_2	CH_2NH	2	1	-	
39	Pr	H	H	H	H	H	CH_2	CH_2NH	2	1	-	
40	Et	H	H	H	H	H	NCHO	CH_2CH_2	2	0	-	
41	Et	H	H	H	H	H	NH	CH_2CH_2	2	0	-	
42	Pr	H	H	H	H	H	NCHO	CH_2CH_2	2	0	-	
43	Pr	H	H	H	H	H	NH	CH_2CH_2	2	0	-	
44	Me	H	Ph	H	H	H	CH_2	CH_2CH_2	2	0	=	
45	Et	H	Ph	H	H	H	CH_2	CH_2CH_2	2	0	=	
46	Pr	H	Ph	H	H	H	CH_2	CH_2CH_2	2	0	=	

Me: methyl
Et: ethyl
Pr: propyl
Ph: phenyl

Example 47

(E)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene) ethylamine

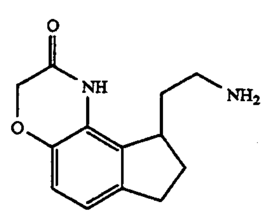


In substantially the same manner as in Example 27, the title compound was produced from (E)-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile (yield 65%) as an oily product.

NMR ($CDCl_3$) δ: 2.61–2.78 (2H, m), 2.80–2.94 (2H, m), 3.20–3.38 (4H, m), 4.56 (2H, t, J=8.8 Hz), 5.83 (1H, m), 6.60 (1H, d, J=8.1 Hz), 6.99 (1H, d, J=8.1 Hz), hidden (2H)

Example 48

9-(2-aminoethyl)-1,7,8,9-tetrahydroindeno[5,4-b)[1,4] oxazin-2(3H)-one

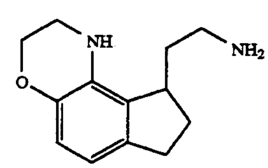


(E)-(1,2,3,7,8,9-Hexahydro-2-oxoindeno[5,4-bj[1,4] oxazin-9-ylidene)acetonitrile (3.0 g, 13.3 mmol.) and Raney nickel (14.0 g) were suspended in a saturated ammonia/ethanol solution (300 mL). The suspension was stirred for 6 hours at 40° C. under hydrogen atmosphere (5 kgf/cm^2). The reaction mixture was cooled, and, then, the Raney nickel catalyst was filtered off. From the filtrate, the solvent was distilled off under reduced pressure to leave an oily residue. The residue was poured into 2N HCl, which was washed with ethyl acetate. The pH of the aqueous layer was adjusted to 10 with a 4N aqueous solution of sodium hydroxide. The organic matter was extracted from the aqueous layer with a mixture solvent of chloroform/methanol (10:1). The extract solution was dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate/isopropyl ether to afford the title compound (yield 1.9 g, 62%).

m.p.: 128–134° C. (recrystallized from ethyl acetate/isopropyl ether); NMR ($CDCl_3$) δ: 1.40–1.90 (6H, m), 2.20–2.50 (2H, m), 2.70 (1H, dd, J=8.0 & 15.4 Hz), 2.90–3.00 (2H, m), 3.40 (1H, q, J=7.9 Hz), 4.44 (1H, d, J=15.0 Hz), 4.58 (1H, d, J=15.0 Hz), 6.75 (1H, d, J=8.0 Hz), 6.79 (1H, d, J=8.0 Hz)

Example 49

2-(1,2,3,7,8,9-hexahydroindeno[5,4-b](1,4]oxazin-9-yl) ethylamine

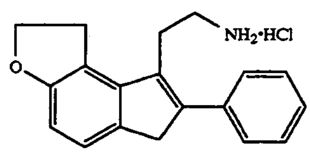


In substantially the same manner as in Example 38, the title compound was produced from 9-(2-aminoethyl)-1,7,8,9- tetrahydroindeno[5,4-b][1,4]oxazin-2-(3H)-one (yield 80%) as an oily product.

NMR ($CDCl_3$) δ: 1.10–3.20 (12H, m), 3.41 (2H, m), 4.20 (2H, m), 6.49 (1H, d, J=8.0 Hz), 6.61 (1H, d, J=8.0 Hz)

Example 50

2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl) ethylamine hydrochloride



A mixture of (E)-(1,6,7,8-tetrahydro-7-phenyl-2H-indeno [5,4-b]furan-8-ylidene)acetonitrile and (1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)acetonitrile (0.815 mg, 2.98 mmol) was hydrogenated (5 kgf/cm^2) on Raney cobalt (2.8 g) in saturated ammonia/ethanol (250 ml) at room temperature for 6 hours. The catalyst was filtered off and the filtrate was concentrated. The residue was diluted with water and extracted with 10% methanol/chloroform. The extract was washed with brine and water, dried over anhydrous magnesium sulfate and evaporated. The residue was dissolved in saturated hydrogen chloride/ethanol (20 ml) and stirred for 1 hour at 80° C. After cooling the solvent was evaporated. The residue was recrystallized from ethanol to afford the title compound (yield 390 mg, 42%).

m.p.: 165–168° C. (recrystallized from ethanol); NMR ($CDCl_3$) δ: 2.87–3.14 (4H, m), 3.51 (2H, t, J=8.4 Hz), 3.72 (2H, s), 4.58 (2H, t, J=8.4 Hz), 6.63 (1H, d, J=7.9 Hz), 7.19 (1H, d, J=7.9 Hz), 7.30–7.58 (5H, m), 8.33 (2H, br s)

Formulation Example 1

(1) Compound obtained in Example 1	10.0 g
(2) Lactose	60.0 g
(3) Corn starch	35.0 g
(4) Gelatin	3.0 g
(5) Magnesium stearate	2.0 g

A mixture comprised of 10.0 g of the compound obtained in Example 1, 60.0 g of lactose and 35.0 g of corn starch was granulated with 30 ml of aqueous 10 wt.% gelatin solution (3.0 g as gelatin) by sieving through a 1 mm-mesh sieve, then dried and again sieved. The resulting granules were mixed with 2.0 g of magnesium stearate and then formed into tablets. The resulting core tablets were coated with a sugar coating of an aqueous suspension comprising sucrose, titanium dioxide, talc and arabic gum. The thus-coated tablets were glazed with bees wax. Thus, obtained were 1000 sugar-coated tablets.

Formulation Example 2

(1) Compound obtained in Example 1	10.0 g
(2) Lactose	70.0 g
(3) Corn starch	50.0 g
(4) Soluble starch	7.0 g
(5) Magnesium stearate	3.0 g

10.0 g of the compound obtained in Example 1 and 3.0 g of magnesium stearate were granulated with 70 ml of an aqueous solution of soluble starch (7.0 g as soluble starch), then dried and mixed with 70.0 g of lactose and 50.0 g of corn starch. The mixture formed into 1000 tablets.

Formulation Example 3

(1) Compound obtained in Example 19	1.0 g
(2) Lactose	60.0 g
(3) Corn starch	35.0 g
(4) Gelatin	3.0 g
(5) Magnesium stearate	2.0 g

A mixture comprised of 1.0 g of the compound obtained in Example 19, 60.0 g of lactose and 35.0 g of corn starch was granulated with 30 ml of aqueous 10 wt. % gelatin solution (3.0 g as gelatin) by sieving through a 1 mm-mesh sieve, then dried and again sieved. The resulting granules were mixed with 2.0 g of magnesium stearate and then formed into tablets. The resulting core tablets were coated with a sugar coating of an aqueous suspension comprising sucrose, titanium dioxide, talc and arabic gum. The thus-coated tablets were glazed with bees wax. Thus, obtained were 1000 sugar-coated tablets.

Experimental Example 1

Inhibition of 2-[^{125}I]iodomelatonin binding activity.

The forebrains of 7-day-old chicken (white leghorn) were homogenized with ice-cold assay buffer (50 mM Tris-HCl, pH 7.7 at 25° C.) and centrifuged at 44,000×g for 10 minutes at 4° C. The pellet was washed once with the same buffer and storred at −30° C. until use. For the assay, the frozen tissue pellet was thawed and homogenized with the assay buffer to make a protein concentration of 0.3–0.4 mg/ml. An 0.4 ml aliquot of this homogenate was incubated with a test compound and 80 pM 2-[^{125}I]iodomelatonin in a total volume of 0.5 ml for 90 minutes at 25° C. The reaction was terminated by adding 3 ml of ice-cold assay buffer immediately followed by vaccum filtration on Whatman GF/B which was further washed twice with 3 ml of ice-cold assay buffer. The radioactivity on the filter was determined by means of γ-counter. Specific binding was calculated by subtracting non-specific binding which was determined in the presence of 10^{-5}M melatonin. The 50% inhibiting concentration (IC_{50}) was determined by the log-probit analysis. The results are shown in Table 3.

TABLE 3

Action of inhibiting 2-[^{125}I]iodomelatonin binding

Compounds of Example	IC_{50} (nM)
1	0.28
2	0.13
3	0.46
4	0.13
5	0.082
7	0.46
8	0.22
11	0.048
13	0.12
14	0.24
15	0.1
16	0.095
Melatonin	0.68

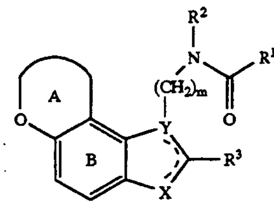
From the results in Table 3 above, it is understood that the compound (I) of the present invention has excellent melatonin receptor-agonistic activity.

As has been described in detail and demonstrated concretely, the compound (I) of the present invention or a salt thereof has excellent binding affinity for melatonin receptor. Therefore, the present invention provides medicines which are clinically useful for preventing and curing

various disorders associated with melatonin activity in vivo. In addition, the compound (I) of the present invention or a salt thereof has excellent in vivo behavior and have excellent solubility in water.

We claim:

1. A compound of the formula:



wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;

R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group;

R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

X represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y represents C, CH or N, provided that when X is CH_2, Y is C or CH;

$\overline{.........}$ represents a single bond or a double bond;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring; and

m represents an integer of 1 to 4, or a salt thereof.

2. A compound as claimed in claim 1, wherein R^1 is (i) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkylcarbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino,

(ii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, or

(iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11} aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^2 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

R^3 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11} aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^4 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-16} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

ring A is a 5- to 7-membered heterocyclic group optionally containing, besides carbon atoms and an oxygen atom, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 4 substituents selected from the

group consisting of (i) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (ii) a halogen, (iii) C_{1-6} alkoxy, (iv) C_{6-10} aryloxy, (v) formyl, (vi) C_{1-6} alkyl-carbonyl, (vii) C_{6-10} aryl-carbonyl, (viii) formyloxy, (ix) C_{1-6} alkyl-carbonyloxy, (x) C_{6-10} aryl-carbonyloxy, (xi) carboxyl, (xii) C_{1-6} alkoxy-carbonyl, (xiii) C_{7-11} aralkyloxy-carbonyl, (xiv) carbamoyl, (xv) an optionally halogenated C_{1-4} alkyl, (xvi) oxo, (xvii) amidino, (xviii) imino, (xix) amino, (xx) mono-C_{1-4} alkylamino, (xxi) di-C_{1-4} alkylamino, (xxii) 3- to 6-membered cyclic amino, (xxiii) C_{1-3} alkylenedioxy, (xxiv) hydroxy, (xxv) nitro, (xxvi) cyano, (xxvii) mercapto, (xxviii) sulfo, (xxix) sulfino, (xxx) phosphono, (xxxi) sulfamoyl, (xxxii) mono-C_{1-6} alkylsulfamoyl, (xxxiii) di-C_{1-6} alkylsulfamoyl, (xxxiv) C_{1-6} alkylthio, (xxxv) C_{6-10} arylthio, (xxxvi) C_{1-6} alkylsulfinyl, (xxxvii) C_{6-10} arylsulfinyl, (xxxviii) C_{1-6} alkylsulfonyl and (xxxix) C_{6-10} arylsulfonyl; and

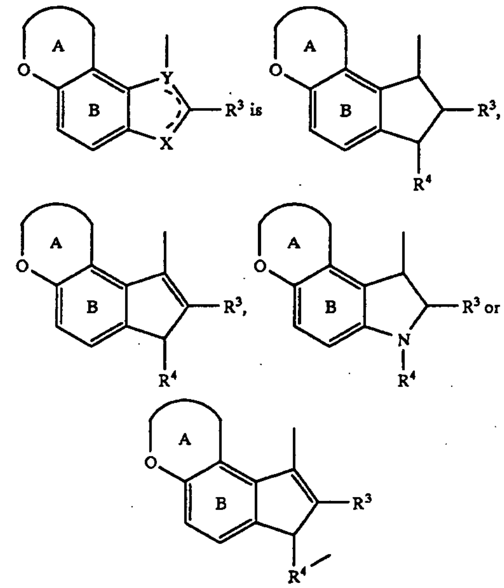
ring B is a benzene ring which may be substituted by 1 or 2 substituents selected from the group consisting of

(i) a halogen,

(ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{16} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino,

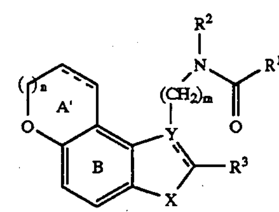
(iii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (iv) a C_{1-6} alkanoylamino group, (v) a C_{1-6} alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (vi) a C_{1-3} alkylenedioxy group.

3. A compound as claimed in claim 1, wherein



wherein $R^{4'}$ is an optionally substituted hydrocarbon group.

4. A compound as claimed in claim 1 which is a compound of the formula:



wherein ring A' is an optionally substituted, oxygen-containing heterocyclic ring;

n is an integer of 0 to 2;

---- and .... are independently a single bond or a double bond.

5. A compound as claimed in claim 1, wherein R^1 is

(i) an optionally substituted C_{1-6} alkyl group,

(ii) an optionally substituted C_{3-6} cycloalkyl group,

(iii) an optionally substituted C_{2-6} alkenyl group,

(iv) an optionally substituted C_{6-14} aryl group,

(v) an optionally substituted mono- or di-C_{1-6} alkylamino group,

(vi) an optionally substituted C_{6-14} arylamino group or

(vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group.

6. A compound as claimed in claim 1, wherein R^1 is an optionally halogenated C_{1-6} alkyl group.

7. A compound as claimed in claim 1, wherein R^2 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

8. A compound as claimed in claim 1, wherein R^2 is a hydrogen atom.

9. A compound as claimed in claim 1, wherein R^3 is a hydrogen atom or an optionally substituted hydrocarbon group.

10. A compound as claimed in claim 1, wherein R^3 is a hydrogen atom.

11. A compound as claimed in claim 1, wherein R^4 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

12. A compound as claimed in claim 1, wherein X is CHR^4.

13. A compound as claimed in claim 1, wherein X is CHR^4 and .... is a single bond.

14. A compound as claimed in claim 13, wherein X is CH_2.

15. A compound as claimed in claim 1, wherein X is NR^4.

16. A compound as claimed in claim 1, wherein Y is C or CH.

17. A compound as claimed in claim 1, wherein Y is CH.

18. A compound as claimed in claim 1, wherein m is 2.

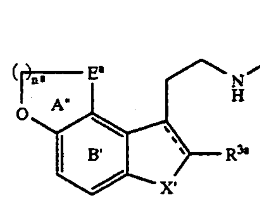
19. A compound as claimed in claim 1, wherein ring A is a tetrahydrofuran ring.

20. A compound as claimed in claim 1, wherein ring A is unsubstituted.

21. A compound as claimed in claim 1, wherein ring B is unsubstituted.

22. A compound as claimed in claim 4, wherein n is 0 or 1.

23. A compound as claimed in claim 1 which is a compound of the formula:



wherein R^{1b} is C_{1-6} alkyl,

X' is CH_2, NH or NCHO,

.... is a single bond or double bond,

R^{3a} is a hydrogen atom or phenyl,

E^a is CH_2CH_2, CH=CH, CH_2O, CH=N, CONH or CH_2NH,

n^a is 0 or 1,

ring A" is a 5- or 6-membered oxgen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and

ring B' is a benzene ring which may be substituted by a halogen.

24. A compound claimed in claim 23, wherein .... is single bond and X' is NH.

25. A compound claimed in claim 1, which is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

26. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide.

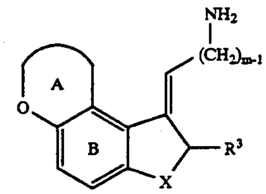
27. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide.

28. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

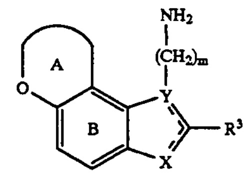
29. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

30. A process for producing a compound as claimed in claim 1, which comprises:

reacting a compound of the formula (i):



or a salt thereof, or (ii):



or a salt thereof, with a compound of the formula:

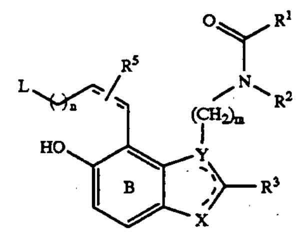
R^1COOH

or a salt or a reactive derivative thereof; and

if necessary, subjecting the resultant compound to reduction and/or alkylation.

31. A process for producing a compound as claimed in claim 4, which comprises:

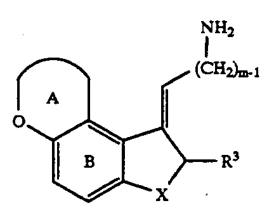
subjecting to cyclization a compound of the formula:



wherein R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxy group, a nitro group, a cyano group or an optionally substituted amino group; L represents a leaving group, or a salt thereof; and

if necessary, subjecting the resultant compound to reduction.

32. A compound of the formula:



wherein R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

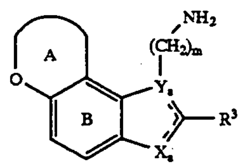
x represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring; and

m represents an integer of 1 to 4, or a salt thereof.

33. A compound of the formula:



wherein X^a represents CHR^{4a}, NR^{4a}, O or S in which R^{4a} represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y^a represents C, CH or N, provided that when X^a is NH or NCH_3, Y^a is CH or N;

$\overline{....}$ represents a single bond or a double bond;

R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene ring; and

m represents an integer of 1 to 4, or a salt thereof.

34. A pharmaceutical composition which comprises a compound as claimed in claim **1** or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

35. A composition as claimed in claim **34** wherein said compound or said pharmaceutically acceptable salt has a binding affinity for melatonin receptor.

36. Method for treating or preventing diseases related to the action of melatonin in mammals which comprises administrating to a subject in need thereof a therapeutically effective amount of a composition as claimed in claim **35**.

37. A method as claimed in claim **36** which regulates circadian rhythm.

38. A method as claimed in claim **36** which regulates sleep-awake rhythm.

39. A method as claimed in claim **36** which regulates time zone change syndrome.

40. A method as claimed in claim **36** which treats or prevents sleep disorders.

41. A process of manufacturing a pharmaceutical composition comprising the steps of selecting a compound or pharmaceutically acceptable salt of claim **1** and admixing said compound or salt with a pharmaceutically acceptable carrier.

* * * * *

EXHIBIT F.

A copy of the USPTO Maintenance Fee Statement for U.S. Patent 6,034,239.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 197

COMPUTER PATENT ANNUITIES
225 REINEKERS LANE
SUITE 400
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,034,239	**$890.00**	**$0.00**	**08/812,168**	**03/07/00**	**03/06/97**	**04**	**NO**	**PAID**	**92.2379**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

RAMPS 08/25/2005 05:35:08 PM EDT

EXHIBIT G.

A copy of letter acknowledging the receipt of the IND for ramelteon and assigned application number IND 58,136 by the FDA on April 5, 1999.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,136

Takeda America Reserch & Development Center, INC.
Attn:Mikihiko Obayashi, Ph,D.
101 Carnegie Center, Suite 207
Princeton, NJ 08540

APR 8 1999

COPY

Dear Dr.Obayashi:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 58,136

Sponsor: Takeda America Reserch & Development Center, INC.

Name of Drug: TAK-375

Date of Submission: March 31, 1999

Date of Receipt: April 05, 1999

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgment letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of information (21 CFR 312.32(c)(2)), (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15

calendar days after initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please contact Ms. Melaine Shin, R.Ph., Regulatory Management Officer at (301) 594-5511.

Sincerely yours,

John S. Purvis

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

EXHIBIT H.

H1) A copy of letter from Takeda America Research & Development Company, Inc. to FDA informing the agency of pending transfer of IND to Takeda Pharmaceuticals America, Inc. dated August 11, 2000.

Takeda

TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

104 CARNEGIE CENTER•SUITE 201
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

August 11, 2000

Russell Katz, M.D., Director
Division of Neuropharmacological
Drug Products (HFD-120)
Center Document Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

<u>Subject:</u> **IND 58,136 TAK-375**
Transfer of Sponsorship
Serial No. 022

Dear Dr. Katz:

Please be advised that Takeda America Research and Development Center, Inc. is in the process of transferring its pharmaceutical research and development operations in Princeton, New Jersey to its Lincolnshire, Illinois affiliate, Takeda Pharmaceuticals America, Inc. As part of this process, effective August 14, 2000, Takeda R & D Center, Inc. transfers ownership of IND 58, 136 to Takeda Pharmaceuticals America, Inc.

Takeda America Research & Development Center, Inc.'s copy of the complete Investigational New Drug Application, including all amendments, annual reports, and communications with the Division, has been given to the new owner.

The contact at Takeda Pharmaceuticals America, Inc., regarding this submission, is W. Wendell Cheatham, M.D., Vice President, Medical and Regulatory Affairs. Should you require any additional information, please do not hesitate to contact the undersigned.

Sincerely,

John T. Zenno
Director, Regulatory Affairs and Quality Assurance

Copy to: Dr. Mikihiko Obayashi, Ph.D.
Dr. W. Wendell Cheatham, M.D.
Ms. Linda Peters, MS

H2) A copy of letter from Takeda Pharmaceuticals America, Inc. to FDA informing the agency of pending transfer of IND from Takeda America Research & Development Company, Inc. dated August 18, 2000.

475 Half Day Road • Suite 500
Lincolnshire, Illinois 60069
p/ 847.383.3000

TAKEDA PHARMACEUTICALS AMERICA, INC.

August18, 2000

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products HFD-120
Center for Drug Evaluation & Research
Document Control Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND 58,136
TAK-375
Serial No. 023

Other
Notification of Change
Of IND Ownership

Dear Dr. Katz:

The purpose of this communication is to inform the Agency of a change in ownership of the above-referenced Investigational New Drug Application (IND). All rights and responsibilities to the application have been transferred from Takeda America Research & Development Center, Inc., Princeton, NJ to Takeda Pharmaceuticals America, Inc. (TPA), Lincolnshire, IL. TPA commits to all agreements, promises and conditions made by Takeda America Research & Development Center Inc., as contained in the IND. This change in ownership is effective as of the date of this letter. Please note that the parent corporation of the two companies, Takeda Chemical Industries, Ltd., Japan has not changed with this transfer.

TPA has received a copy of the initial IND, all amendments, and all correspondence with the Division from Takeda Research & Development Center, Inc.

The name and address of the contact person at TPA is:

Ms. Linda J. Peters, MS
Associate Director, Regulatory Affairs
Takeda Pharmaceuticals America, Inc.
475 Half Day Road, Suite 500
Lincolnshire, IL 60069
(847) 383-3070
(847) 383-3143 (fax)

Ms. Peters has a Master's Degree in Animal Science/Physiology and over 10 years of experience in the pharmaceutical industry.

TPA commits to amend the IND within 60 days to cover any changes in the IND resulting from the new ownership. Also, all active investigators will be notified of the change.

Should you require any additional information, please do not hesitate to contact the undersigned.

Sincerely yours,

Alan MacKenzie
President
Takeda Pharmaceuticals America, Inc.

Cc: Saburo Hamanaka, Takeda Pharmaceuticals America, Inc.,
Mikihiko Obayashi, Takeda America Research & Development Center, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **INVESTIGATIONAL NEW DRUG APPLICATION (IND)** *(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*	*Form Approved:* OMB No. 0910-0014. *Expiration Date:* September 30, 2002. *See OMB Statement on Reverse.* NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).
1. NAME OF SPONSOR Takeda Pharmaceuticals America, Inc.	2. DATE OF SUBMISSION August 18, 2000
3. ADDRESS *(Number, Street, City, State and Zip Code)* 475 Half Day Road, Ste 500 Lincolnshire, IL 60069	4. TELEPHONE NUMBER *(Include Area Code)* 847/383-3002
5 NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)* TAK-375	6. IND NUMBER *(If previously assigned)* 58,136

7. INDICATION(S) *(Covered by this submission)*

N/A

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:

N/A ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER: *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION

N/A

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***	SERIAL NUMBER 0 2 3

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☒ OTHER Notification of change of IND Ownership *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environment assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☒ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED. N/A

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

N/A

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

N/A

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Alan MacKenzie	Alan MacKenzie	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
475 Half Day Road, Ste 500 Lincolnshire, IL 60069	847/383-3002	August 18, 2000

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20859

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

H3) A copy of letter from Takeda Pharmaceuticals North America, Inc. to the FDA informing the agency of the name change of the IND holder from Takeda Pharmaceuticals America, Inc. to Takeda Pharmaceuticals North America, Inc., dated January 2, 2001.

475 Half Day Road • Suite 500
Lincolnshire, Illinois 60069
p/ 847.383.3000

TAKEDA PHARMACEUTICALS AMERICA, INC.

January 2, 2001

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation & Research
Central Document Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND No. 58,136
TAK-375
SERIAL NO. 027

Other
Name Change of Company

Dear Dr. Katz:

Pursuant to 21 CFR § 312.31 (a), Takeda Pharmaceuticals North America, Inc. submits the following information to the above mentioned IND.

Takeda Pharmaceuticals America, Inc. has changed its name to Takeda Pharmaceuticals North America, Inc. All other information, such as mailing address, phone numbers and responsible personnel for this IND has remained the same.

Should you have any questions, or require additional information, please do not hesitate to contact the undersigned.

Sincerely,

Robert M. Pilson, RPh
Manager, Regulatory Compliance
Takeda Pharmaceuticals North America, Inc.
P/ 847-383-3023
F/ 847-383-3143

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **INVESTIGATIONAL NEW DRUG APPLICATION (IND)** *(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*	*Form Approved:* OMB No. 0910-0014. *Expiration Date:* September 30, 2002. *See OMB Statement on Reverse.* **NOTE:** No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).
1. NAME OF SPONSOR Takeda Pharmaceuticals North America, Inc.	2. DATE OF SUBMISSION January 2, 2001
3. ADDRESS *(Number, Street, City, State and Zip Code)* 475 Half Day Road, Ste 500 Lincolnshire, IL 60069	4. TELEPHONE NUMBER *(Include Area Code)* 847/383-3023
5 NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)* TAK-375	6. IND NUMBER *(If previously assigned)* 58,136

7. INDICATION(S) *(Covered by this submission)*
N/A

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER: ____________ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION

10. ***IND submission should be consebcutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or corredpondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***	SERIAL NUMBER 0 2 7

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☒ OTHER Name Change of Company *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [ ] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [ ] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environment assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED. N/A

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

N/A

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

N/A

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Robert M. Pilson, RPh	Bill Pilson	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	**19. TELEPHONE NUMBER** *(Include Area Code)*	**20. DATE**
475 Half Day Road, Ste 500 Lincolnshire, IL 60069	847/383-3023	January 2, 2001

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

EXHIBIT I.

A copy of the letter from Takeda Pharmaceuticals North America, Inc. to the FDA informing the agency of the pending transfer of the IND to Takeda Global Research and Development, Inc. dated January 9, 2004.

January 9, 2004

Robert Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170
Central Document Room 8B45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND 58,136
Ramelteon (TAK-375)
Serial No. 134

General Correspondence

Dear Dr. Rappaport:

Takeda Pharmaceuticals North America, Inc. (TPNA), the sponsor of the subject IND, hereby informs the Agency of a transfer of ownership and sponsorship of the IND to Takeda Global Research & Development Center, Inc. (TGRD). TGRD is a newly created, wholly owned subsidiary of TPNA. The individuals that were responsible for the conduct of the clinical trials and for regulatory affairs have been transferred to the new company so the contact persons will remain the same. If any additional information is necessary, please contact me.

Sincerely,

Leslie R. Koehler
Associate Director
Regulatory Affairs
TGRD

LK:lk

TAKEDA GLOBAL RESEARCH & DEVELOPMENT CENTER, INC.
475 Half Day Road Lincolnshire, Illinois 60069 Phone: 847-383-3000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSER
Takeda Global Research & Development Center, Inc.

2. DATE OF SUBMISSION
1/9/04

3. ADDRESS *(Number, Street, City, State and Zip Code)*
475 Half Day Road
Lincolnshire, IL 60069

4. TELEPHONE NUMBER *(Include Area Code)*
847-383-3522

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Ramelteon (TAK-375)

6. IND NUMBER *(If previously assigned)*
58,136

7. INDICATION(S) *(Covered by this submission)*
Treatment of Sleep Disorders

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER ________ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
58,136

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 1 3 4

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER ________ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

David Kim, Clinical Program Manager, Clinical Research

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Stephen M. Sainati, M.D., Ph.D., Vice President, Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Leslie Koehler	Leslie Koehler	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
475 Half Day Road Lincolnshire, IL 60069	847-383-3522	1/9/04

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

EXHIBIT J.

A copy of letter acknowledging the receipt of the NDA for LUNIVIA™ (ramelteon), the name of which was changed to ROZEREM™ (ramelteon), and assigned application number NDA 21-782 by the FDA on September 22, 2004.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-782

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, Illinois 60069

Attention: Steve Danielson
Manager, Regulatory Affairs

Dear Mr. Danielson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lunivia (ramelteon) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	September 21, 2004
Date of Receipt:	September 22, 2004
Our Reference Number:	NDA 21-782

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 21, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 22, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sara Stradley
10/21/04 08:01:29 AM

EXHIBIT K.

A Brief Summary of the significant activities undertaken and the significant dates thereof, by and or for the marketing applicant during the applicable regulatory review period.

K1) IND related activities

Serial No.	Date	Subject	Reports Filed			
0	31-Mar-99	Initial IND	M-11-120	M-11-78	M-11-74	M-11-18
			M-11-106	M-11-11	M-11-73	M-11-20
			M-11-95	M-11-27	M-11-36	M-11-22
			M-11-102	M-11-26	M-11-103	M-11-98
			M-11-49	M-11-26-1	M-11-13	M-11-52
			M-11-50	M-11-37	M-11-19	
			M-11-16	M-11-38	M-11-19-1	
1	08-Apr-99	Correcting that CRO will no be used, and submission of PNFP-001 protocol	PNFP-001 protocol			
2	21-Apr-99	Response to CMC Questions	N/A			
3	26-May-99	Response to Clinical Hold	M-11-138			
			M-11-137			
			M-11-136			
			M-11-135			
4	16-Jun-99	Response to CMC questions obtained in a phone conversation on 10-11 June with FDA	N/A			
5	24-Jun-99	Resolution of Clinical Hold: Response to FDA that TPNA will include a total impurity limit of 1.5% for the four tablet strenghts	N/A			
6	01-Jul-99	Submission of updated specifications to include the 1.5% total impurity limit	M-11-140			
			M-11-141			
			M-11-142			
			M-11-143			
			CoAs			
7	24-Sep-99	Revise IB to include teratogenic and embryotoxic at doses 40mg/kg and higher	IB			
8	11-Oct-99	Amendment 1 to protocol PNFP-001	PNFP-001 Amendment 1			
9	11-Oct-99	Amendment 2 to protocol PNFP-001	PNFP-001 Amendment 2			

Serial No.	Date	Subject	Reports Filed			
10	22-Dec-99	Amendment 3 to protocol PNFP-001 including higher doses of 16 and 32 mg, CPH-001	PNFP-001 Amendment 3			
			CPH-001 Summary Report			
			Tox summary			
11	06-Jan-00	change of address	N/A			
12	04-Apr-00	Request for CAC review on the two protocols and Tox info amendment. Attached to this are the minutes from the Executive CAC review meeting which states that they could not concur on our dose levels. The minutes indicate that we can submit preliminary data from 6mo. along with the protocols and ask for review again. Problem: The minutes suggest that the original protocols were submitted requesting CAC review, however I cannot find any serial amendment or FDA correspondence documenting the submission, or the additional reports the CAC requested.	M-11-163 (Study B2873) M-11-176 (Study B-2873) M-11-178 (Study B-4203) Protocol B-4204 Protocol B-4416			
13	07-Apr-00	Pharm/Tox Information Amendment	M-11-110			
			M-11-171			
			M-11-56			
			M-11-192			
			M-11-166			
			M-11-185			
			M-11-186			
			M-11-189			
14	24-Apr-00	New protocol PNFP-002.1 and investigator submission	PNFP-002.1			

Serial No.	Date	Subject	Reports Filed			
15-18	multiple	Investigator submission for PNFP-002.1				
19	13-Jun-00	Pharm/Tox Information Amendment	M-11-168	M-11-210	M-11-227	
			M-11-187	M-11-212	M-11-230	
			M-11-173	M-11-211		
20	03-Aug-00	Annual Report	M-11-195	M-11-213		
			M-11-196	M-11-225		
			M-11-197	M-11-228		
			M-11-198	M-11-229		
			M-11-194	M-11-226		
			M-11-214	M-11-231		
21	09-Aug-00	Amendment 2 to protocol PNFP-002.2	PNFP-002.2			
22	11-Aug-00	Transfer of Sponsorship from Jersey to TPNA				
23	18-Aug-00	TPNA accepts ownership				
24	03-Oct-00	Response to requests for 6 month data on the rat/mouse CA studies by the CAC Committee; CAC Meeting Minutes are Attached	M-11-247			
			M-11-244			
25	06-Dec-00	PNFP.002.3 Protocol Amendment				
26	11-Dec-00	New Investigators PNFP-002				
27	02-Jan-01	Change in name from TPA to TPNA				
28	08-Mar-01	CMC Amendment providing required documents for 8 mg tablet. Use will begin with -003 & -004	M-11-208 M-11-269 M-11-270			

Serial No.	Date	Subject	Reports Filed			
29	12-Mar-01	Protocol 01-01-TL-375-003 Submission				
30	29-Mar-01	Revised Box 13 for 01-01-TL-375-003				
31	10-Apr-01	Protocol 01-01-TL-375-004 Submission				
32	26-Apr-01	Response to FDA Request (requesting referenced reports)	IB 1999	PNFP-001.3		
			CPH-001			
			Flash results for CPH-001, 002, 006			
33	23-May-01	Pharm/Tox Information Amendment	M-11-13.1	M-11-192.1		
			M-11-37	M-11-232		
			M-11-103.1	M-11-268		
			M-11-110	M-11-271.1		
			M-11-163	M-11-294		
			M-11-188	M-11-295		
34	25-May-01	CSR PNFP-001				
35	30-May-01	Protocol 01-01-TL-375-005				
36	31-May-01	To correct the CSR number from 01-01-TL-375-001 to PNFP-001				
37	08-Jun-01	CSR PNFP-002				
38	6/26/001	Annual report for 4/30/00 to 4/30/01				

Serial No.	Date	Subject	Reports Filed			
39	26-Jun-01	Revised Formulation of Drug Product Submitted 4, 8, 16, 32 mg tablet and placebo with new film coating.	M-11-00280 M-11-00275 M-11-00276 M-11-00277 M-11-00278 M-11-00279, M-11-00285 M-11-00285, M-11-00286, M-11-00287 M-11-00288, M-11-00289, M-11-00309 M-11-00310, M-11-00311, M-11-00312			
40	16-Jul-01	Response to FDA Questions regarding protocols -003, -004, -005				
41	10-Aug-01	Request for EOPII Meeting for CRSD	Briefing Doc			
42	19-Sep-01	01-01-TL-375-005, Amendment 1				
43	11-Oct-01	Pharmacology/Toxicology; FSR EC-002	M-11-121, M-11-122, M-11-123,			
44	16-Oct-01	CRSD Briefing Document				
45	31-Oct-01	01-01-TL-375-005, Amendment 2; 01-01-TL-375-007 protocol; investigators				
46	08-Nov-01	01-01-TL-375-006 & Amendment 1 to -006, 01-01-TL-375-008				

Serial No.	Date	Subject	Reports Filed			
47	16-Nov-01	Informing FDA of the identification of a new impurity U-6 found upon retest. This impurity was used in clinical study 01-01-TL-375-003 & -004	M-11-332			
48	12-Dec-01	01-01-TL-375-008, Amendment 1; 01-01-TL-375-007, Amendment 1; IB, investigator, Non-clinical update	M-11-244, M-11-132, M-11-133, M-11-327			
49	11-Jan-02	Minutes from 11/8 End-of-Phase II Meeting for CRSD				
50	11-Mar-02	01-02-TL-375-009; 01-01-TL-375-006, Amendment 1				
51	23-Apr-02	EOP II Meeting Request for Insomnia				
52	31-May-02	Pharm/Tox Info Amendment & CTR 01-01-TL-375-003	M-11-340, M-11-347, M-11-348, M-11-349, M-11-353, M-11-354, M-11-356,			
53	14-Jun-02	EOPII Insomnia Briefing Document				

Serial No.	Date	Subject	Reports Filed			
54	26-Jun-02	Annual Report May 01 through April 02 including IB and -009 Amendment 1	M-11-299, M-11-300, M-11-301, M-11-302, M-11-303, M-11-358, M-11-359, M-11-360, M-11-361			
55	08-Aug-02	IND Safety Report, CA study results, FDA Review Requested	Summary of preliminary results & IND safety letter			
56	21-Aug-02	01-02-TL-375-017 Protocol, Amendment 1, 01-02-TL-375-022, Amendment 1 Protocol Submissions (Studies started with Amendment 1 incorporating CA info)				
57	03-Sep-02	01-02-TL-375-014 Protocol Submission				
58	10-Sep-02	01-02-TL-375-026 Protocol Submission; Non-clinical update	M-11-388, M-11-389			
59	10-Sep-02	At EOPII, FDA requested endocrine monitoring during Phase III. This submission includes the proposed Endocrine Monitoring Plan with synopsis to follow on 10/11/02	M-11-176			

Serial No.	Date	Subject	Reports Filed			
60	18-Sep-02	Revised API synthesis; use begins 9/02 with 01-02-TL-375-022 & 01-02-TL-375-017	M-11-230.001 M-11-226.001 M-11-228.001 M-11-229.001 M-11-230.001 M-11-231.001 M-11-372.001 M-11-363			
61	23-Sep-02	01-02-TL-375-024 Protocol Submission				
62	24-Sep-02	EOPII Meeting Minutes for Insomnia; TCR9/19/02 indicates that a teleconference will be held on 10/3 (which was moved to 10/9) to discuss endocrine synopsis				
63	24-Sep-02	01-02-TL-375-027 Protocol Submission				
64	14-Oct-02	New/Revised Investigators				
65	16-Oct-02	10/9/02 Teleconference Meeting Minutes. Commit to FDA to submit the short & long-term endocrine monitoring by 10/28/02				
66	17-Oct-02	New Investigators -017				
67	25-Oct-02	Response to FDA Request for Information: Endocrine Protocol Synopsis				
68	08-Nov-02	Response to FDA Request for Information: Teleconference held 11/7/02, DNDP requested additional endocrine parameters				

Serial No.	Date	Subject	Reports Filed			
69	15-Nov-02	New Protocol Submission: 01-02-TL-375-020, -021, -023, -025; Letter indicates that stat methods described in protocols 20/21 addresses FDA reccomendations				
70	26-Nov-02	End-of-Phase II, CMC Meeting Request				
71	06-Dec-02	November 20, 2002 Teleconference Minutes between DNDP & TPNA regarding Endocrine Proposal and -031/-032 Protocol synopsis				
72	06-Dec-02	01-02-TL-375-017, Amendment 2; Non-clinical; New/revised Investigators	M-11-398, M-11-512			
73	09-Dec-02	01-02-TL-375-022, Amemdment 2 Incorporating endocrine monitoring				
74	13-Dec-02	EOPII, CMC Briefing Document				
75	16-Dec-02	01-02-TL-375-031, -032 Endocrine Short/Long Term Protocol submission				
76	08-Jan-03	Response to FDA questions regarding the EOPII CMC Briefing Document				
77	09-Jan-03	New and Revised Investigators for 01-02-TL-375-017 and -022; clinical study amendment 1 for 01-02-TI-375-024				
78	24-Jan-03	TPNA Minutes from the End of Phase II, CMC teleconference held on January 17, 2003				
79	11-Feb-03	Amendment 1 to protocol 01-02-TL-375-020 and -025; New and Revised Investigators				
80	13-Feb-03	Amendment 1 to protocol 01-02-TL-375-031 and new investigator				
81	18-Feb-03	New protocol and investigators for study 01-02-TL-375-029 and -030				

Serial No.	Date	Subject	Reports Filed			
82	19-Feb-03	Final Reports M-11-00560 and M-11-00561				
83	19-Feb-03	Information Amendment: Pharmacology-Toxicology	M-11-00536, M-11-00557, M-11-00562, M-11-00565			
84	20-Feb-03	Protocol Amendment: 01-02-TL-375-021, Amendment 1, 01-02-TL-375-022, Amendment 3				
85	27-Feb-03	New and Revised Investigators for 01-02-TL-375-020, -021, -022, -023, -025				
86	03-Mar-03	New Protocol and investigators for study 01-02-TL-375-028 and -033				
87	18-Mar-03	Protocol Amendment: 01-02-TL-375-031, Amendment 2, 01-02-TL-375-032, Amendment 1				
88	27-Mar-03	New and Revised Investigators for studies -006, -007, -008, -020, -021, -022, -023, -025, -030, -031				
89	04-Apr-03	New Protocols 01-02-TL-375-015, 01-03-TL-375-034, 01-03-TL-375-035, 01-03-TL-375-036				
90	29-Apr-03	New/Revised Investigators for 01-02-TL-375-017, -020, -021, -022, -023, -025, -028, -032,				
91	02-May-03	Amendmnet 1; 01-02-TL-375-023 Amendment 1, Administrative Change 1; 01-02-TL-375-028 Administrative Change 1; 01-02-TL-375-033 Administrative Change 1; 01-03-TL-375-037 Amendment 1				

Serial No.	Date	Subject	Reports Filed			
92	04-Jun-03	New/Revised Investigators for 01-02-TL-375-009, -017, -020, -021, -022, -023, -025, -028, -030, -032, -036				
93	17-Jun-03	Info Amend : Pharm/Tox	M-11-00563, M-11-00572, M-11-00593, M-11-00594, M-11-00599, 01-02-TL-375-011, 01-02-TL-375-012			
94	27-Jun-03	Info Amend: New protocol 01-02-TL-375-038 and 01-02-TL-375-039/Change in protocol 01-02-TL-375-022 Amendment 4, 01-02-TL-375-032 Amendment 2, 01-02-TL-375-025 Administrative change 1, 01-02-TL-375-035, Administrative Change 1, 01-03-TL-375-037 Administrative Change 1				
95	02-Jul-03	IND Safety Report: Initial: TPA2003A00835				
96	02-Jul-03	Proposed propritary name Lunivia				
97	17-Jul-03	New/Revised Investigators for 01-02-TL-375-020, -022, -025, -032, 01-03-TL-375-038, -039				

Serial No.	Date	Subject	Reports Filed			
98	21-Jul-03	CMC Update - drug product formulation change in the 8mg, 16mg, and placebo Phase III clinical drug supplies. 16 mg tablet and placebo changed grade of hydroxpropyl cellulose from HPC to HPC-SL-T, introduction of red ferric oxide and polyethylene glycol. 8mg tablet and corresponding placebo introduced polyethylene glycol.				
99	22-Jul-03	IND Safety Report - Initial TPA2003A00975				
100	23-Jul-03	General Correspondence - Requested to remain with the Division of Neurophamacological Drug Products.				
101	23-Jul-03	First endocrine and AM Cortisol Report to FDA as requested.				
102	29-Jul-03	Notice of non-Compliance Dr. Hinton (01-02-TL-375-020)				
103	06-Aug-03	New/Revised Investigators for 01-01-TL-375-005, 01-02-TL-375-017, -020, -021, -022, -025, -032				

Serial No.	Date	Subject	Reports Filed			
104	08-Aug-03	New protocol and investigator for 01-02-TL-375-040; Protocol amendments: 01-02-TL-375-015 Amendment 2; 01-02-TL-375-038 Amendment 1; 01-05-TL-375-021 Administrative Change 1; 01-02-TL-375-025 Administrative Change 2; 01-02-TL-375-035 Administrative Change 1;01-02-TL-375-037 Administrative Change 1				
105	20-Aug-03	Pharm/Tox Amendment update	M-11-00606, M-11-00607, M-11-00608, M-11-00609, M-11-00610, M-11-00611, M-11-00612			
106	20-Aug-03	IND Safety Report - Follow up report, TPA2003A00835				
107	21-Aug-03	2003 Annual Report				
108	22-Aug-03	Protocol Amendment 01-02-TL-375-40 Amendment 1				
109	27-Aug-03	IND Safety Report F/up TPA2003A00975				
110	04-Sep-03	New/Revised Investigators				
111	10-Sep-03	IND Safety Report - Initial Reports for TPA2003A01202 and TPA2003A001210				
112	17-Sep-03	1st 120-day Endocrine Report				
113	22-Sep-03	IND Safety Report - Follow up report for TPA2003A01202				

Serial No.	Date	Subject	Reports Filed			
114	25-Sep-03	Protocol Amendment 01-03-TL-375-038 Amendment 2; 01-03-TL-375-039 Amendment 1; 01-02-TL-375-020 Amendment 2; 01-03-TL-375-040 Adminstrative Change 1				
115	26-Sep-03	Final Clinical Trial Report 01-01-TL-375-003 Amendment 1; -005; -006; 01-02-TL-375-024				
116	29-Sep-03	Pre-NDA Meeting Request, CMC				
117	01-Oct-03	New/Revised Investigators				
118	02-Oct-03	Response to FDA, TPNA received an email requesting us to provide the dosage form, strength(s), regimen, and AE informtion in support of our proposed propritary name				
119	27-Oct-03	Respond to questions on protocol 01-02-TL-375-031 and -032 by the Division of Metabolic and Endocrine Drug Products				
120	27-Oct-03	Info Amendment: Pre-NDA, CMC Briefing Document				
121	31-Oct-03	Initial Safety Report TPA2003A01202				
122	04-Nov-03	Correction to Serial 121, re-sbmission of the safety report since the addendum to the IB was not included				
123	07-Nov-03	New/Revised Investigators				
124	07-Nov-03	Protocol Amendment 01-02-TL-375-015 Amendment 3; Final Clinical Trial Report for studies 01-01-TL-375-007; 01-02-TL-375-009; -014; -026; -027				

Serial No.	Date	Subject	Reports Filed			
125	18-Nov-03	IND Initial Safety Report TPA2003A01577				
126	25-Nov-03	Protocol Amendment 01-02-TL-375-032 Amendment 3 and Final Clinical Trial Report for EC004				
127	03-Dec-03	New/Revised Investigators				
128	03-Dec-03	IND Safety Follow up TPA2003A01577				
129	10-Dec-03	Final Clinical Trial Report 01-01-TL-375-008				
130	17-Dec-03	IND Safety Follow-Up TPA2003A01210				
131	22-Dec-03	IND Initial Safety Report PTA2003A01721				
132	31-Dec-03	IND Safety Follow-Up TPA2003A01721				
133	08-Jan-04	Monthly Investigators Dec 2003				
134	09-Jan-04	General Correspondence informing the Agency of the transfer of the IND from TPNA to TGRD				
135	14-Jan-04	Type A Meeting Request; the focus of the meeting will be to discuss alternative methods to document the patient-reported efficacy of ramelteon as a non-anxiolytic sleep agent.				
136	14-Jan-04	TGRD Pre-NDA, CMC Meeting Minutes				

Serial No.	Date	Subject	Reports Filed			
137	29-Jan-04	Amendment - Pharm/Tox	M-11-012.001 M-11-171.001 M-11-00323 M-11-00613 M-11-00616 M-11-00618 M-11-621.001 M-11-00623 M-11-00624			
138	30-Jan-04	Second 120 day Endocrine Report				
139	30-Jan-04	Briefing Document for Special Consderation Mtg Requeste in Serial #135				
140	18-Feb-04	Response to FDA CMC Meeting Minutes noting the following discrepancies: Q1) TGRD reminded FDA that they stated they would stand by the agreement reached with DNDP in term of the starting material designations; Q5) TGRD indicated that we did not agree to a dissolution specifiction of Q = 80% at 15 minutes; Q6)TGRD indicating that FDA minutes did not provide an opportunity to justify site comparability between TIL and TCI manufacturing sites				
141	24-Feb-04	IND Safety Report - Initial TPA2004A00198				
142	01-Mar-04	February 11th Teleconference Meeting minutes				
143	04-Mar-04	March Investigators				

Serial No.	Date	Subject	Reports Filed			
144	20-Apr-04	Informing FDA that we inadvertantly skipped over serial no. 144.				
145	11-Mar-04	IND Safety Report - Follow-Up TPA200301202				
146	17-Mar-04	IND Safety Report - Follow-Up				
147	05-Apr-04	April Investigators				
148	14-Apr-04	Notice of Non-Compliance - Vapnik				
149	15-Apr-04	Pre-NDA Meeting Request - Type B				
150	05-May-04	May Investigators				
151	18-May-04	IND Safety Report - Initial TPA2004A00572				
152	20-May-04	Pre-NDA Briefing Document Submission				
153	25-May-04	IND Safety Report - Follow-Up TPA2004A00572				
154	27-May-04	Third 120-day Endocrine Report				

Serial No.	Date	Subject	Reports Filed			
155	28-May-04	Information Amendment: Pharmacology-Toxicology	M-11-323.001R M-11-560.001A M-11-561.001A M-11-616.001R M-11-00617 M-11-00619 M-11-00620 M-11-00622 M-11-00628 M-11-00629 M-11-00630 M-11-00631 M-11-00632 M-11-00633 M-11-00634 M-11-00635 M-11-00636 M-11-00637 M-11-00638 M-11-00639 M-11-00643 M-11-00644 M-11-00708 M-11-00689 M-11-00690 M-11-00736 M-11-00747 M-11-00748 M-11-00749			
156	07-Jun-04	Protocol 01-04-TL-375-043				
157	08-Jun-04	June Investigators				

Serial No.	Date	Subject	Reports Filed			
158	24-Jun-04	IND Safety Report - Follow-Up TPA2004A00572				
159	12-Jul-04	July Investigators				
160	29-Jul-04	Protocol 01-02-TL-375-022 Amendment 5; 01-04-TL-375-043 Amendment 1				
161	30-Jul-04	August Investigators				
162	09-Sep-04	September Investigators				
163	13-Oct-04	October Investigators				
164	09-Nov-04	November Investigators				
165	08-Dec-04	December Investigators				
166	16-Dec-04	New Protocol 01-04-TL-375-041				
167	22-Dec-04	IND Safety Report - TPA2004A01543				
168	13-Jan-05	IND Safety Report - Follow-Up TPA2004A01543				
169	01-Feb-05	IND Safety Report - Follow-Up TPA2004A01543				
170	04-Feb-05	Monthly Investigators				
171	09-Feb-05	01-04-TL-375-041 Amendment #1				
172	09-Feb-05	IND Safety Report - Follow-Up TPA2004A01543				
173	17-Feb-05	New Protocol and Investigator: 01-04-TL-375-049 Amendment 1; 01-04-TL-375-050				
174	24-Feb-05	New Protocol and Investigator 01-02-TL-375-018; Information Amendment, CMC: 1 and 2 mg				
175	28-Feb-05	New Protocol and Investigator 01-04-TL-375-051				

Serial No.	Date	Subject	Reports Filed			
176	04-Mar-05	Monthly Investigator				
177	15-Mar-05	New Protocol and Investigator 01-04-TL-375-052 and 01-04-TL-375-054				
178	06-Apr-05	Monthly Investigator				
179	15-Apr-05	Corrected the cover letter for Serial 178; Serial 178 incorrectly indentified study 01-02-TL-375-022 instead of 01-04-TL-375-041				
180	15-Apr-05	New Protocol and Investigator 01-04-TL-375-056				
181	04-May-05	May Monthly Investigator				
182	03-Jun-05	June Monthly Investigator				
183	30-Jun-05	July Monthly Investigator and Protocol Amendment 01-04-TL-375-041 Amendment 2				
184	11-Jul-05	New Protocol EC302				
185	04-Aug-05	August Monthly Investigator				

K2) NDA 21-782 related activities

Amendment No.	Date	Submission
0000	9/21/2004	Original NDA
0001	10/4/2004	Updated Debarment Statement
0002	11/16/2004	Submission of Report M-11-19, entire amendment
0003	1/7/2005	Response to FDA request - The original tradename Lunivia was rejected by DMETS and DACCADP. Included in this letter was comments on the labeling for the commenrcial products. This submission included our new tradename proposals (Dorivial and Dormera), and responses to the commercial package labeling.
0004	1/14/2005	Response to FDA Communication - 74 day letter CMC Related Questions
0005	1/20/2005	Submission of the required 120 day (4 month) IAS Safety Update
0006	2/4/2005	Response to FDA communication - Electronic submission of updated commercial package labeling
0007	2/15/2005	Submission of new DMF letter for Print Ink Grey updated by manufacturer
0008	2/22/2005	Response to FDA - Data on spontaneous tumor incidence & alternate sample package for FDA review
0009	3/7/2005	Response to FDA - Repeat submission of 008 in PDF format instead of Excel. Also included is a summary of the historical control data for hepatoblastomas
0010	3/17/2005	Response to FDA - Submission of a table identifying and enumerating the patients that withdrew from study 01-02-TL-375-025
0011	3/23/2005	Response to FDA letter dated March 7, 2005 with comments on the commercial package labeling by DMETS and DACCADP
0012	3/23/2005	Response to FDA - Acknowledgement of the rejection of Dorivia and Dormera and proposal of new tradenames f Abenel and Rozerem for Review
0013	4/4/2005	Response to FDA - Submission of a table identifying and enumerating the patients that withdrew from study 01-02-TL-375-021
0014	4/21/2005	CMC Stability Update
0015	5/12/2005	Response to FDA - Provided requested references
0016	6/1/2005	Provided FDA with background information to support the term "chronosomnotic" as ramelteons descriptive nomenclature
0017	6/15/2005	CMC Request for Clarification to Questions received by email on June 10, 2005 on the Drug Substance & Product
0018	6/22/2005	CMC - Response to FDA questions received by email on June 10, 2005 on the Drug Substance & Product
0019	6/24/2005	CMC Repsone to FDA question regarding BCS Classification

0020	6/28/2005	Response to FDA - Electronic submission of updated commercial package labeling as requested by DMETS and DACCADP (Packaging)
0021	6/30/2005	Response to FDA - Submission of translated batch records and manufacturing directions for the starting material ICN
0022	7/8/2005	CMC - Response to FDA questions received by email on June 10, 2005 on the Drug Substance & Product
0023	7/18/2005	Response to FDA -TGRDs counter proposal to the comments received from FDA on the Package Insert
0024	7/22/2005	Final Package Insert
0025	7/22/2005	Final Package Insert - updated final package insert based on FDAs comments regarding the request to remove the sataement "Product of Japan" from the labeling. TGRDs legal department noted that this was in violation of customs laws and discussions with FDA will continue.
	7/22/2005	FDA Approval Letter
0026	7/26/2005	PDUFA Safety Update

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